EXHIBIT 3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	Confirmation No.: 2895
DeGRADO *et al.*	Art Unit: 1617
Appl. No. 10/801,951	Examiner: Chong, Yong Soo
Filed: March 17, 2004	Atty. Docket: 1694.0630003/JMC/M-R/KHR
For: **Facially Amphiphilic Polymers and Oligomers and Uses Thereof**	

Declaration of David P. Nicolau, Pharm.D., FCCP Under 37 C.F.R. § 1.132

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Sir:

I, the undersigned, Dr. David P. Nicolau, residing at 15 Chandler Drive, South Windsor, CT 06074, USA, declare and state as follows:

1. A current *curriculum vitae* is appended hereto as Exhibit A1.

2. PolyMedix, Inc., the licensee of the above-identified patent application ("patent application") has contracted with Hartford Hospital in Hartford, Connecticut for my research laboratory to test the anti-infective activity of certain compounds that PolyMedix has in development.

3. I received my Pharm.D. degree from the Medical University of South Carolina in 1990. I am currently the Director of the Center for Anti-Infective Research and Development at Hartford Hospital in Hartford, Connecticut. As seen from my attached *curriculum vitae*, I have published extensively and am involved in numerous professional and scientific societies related to

infectious diseases. Based on my education and experience, I am an expert in the field of infectious diseases.

4. I have reviewed the above-captioned patent application, including the description and pending claims, and the final Office Action dated October 30, 2007. I have also reviewed U.S. Patent No. 7,173,102 B2 to DeGrado *et al.* ("the '102 patent").

5. The invention claimed in the patent application relates to a method of treating a microbial infection in an animal by administering an effective amount of a pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent.

6. It is my understanding that the Examiner has rejected the claims as being obvious over the '102 patent on the basis that it would have been obvious to a person of ordinary skill in the art to treat an animal with a microbial infection by administering a pharmaceutical composition containing oligomers described in the '102 patent. Additionally, it is my understanding that based upon the disclosures in the '102 patent, the Examiner alleges a person of ordinary skill in the art would have had a reasonable expectation of success of treating a microbial infection in an animal by administering a pharmaceutical composition containing the preferred oligomers disclosed in the '102 patent.

7. For at least the reasons described below, I respectfully disagree with the Examiner's conclusion that a person of ordinary skill in the art would have been motivated to treat a microbial infection in an animal by administering an effective amount of a pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent,

as claimed in the patent application, based upon the disclosures of the '102 patent. I also disagree with the Examiner's conclusion that a person of ordinary skill in the art would have possessed a reasonable expectation that a microbial infection in an animal could be successfully treated by administering a pharmaceutical composition containing the preferred oligomers disclosed in the '102 patent.

8. First, a person of ordinary skill in the art would not necessarily expect the polymers described in the '102 patent to be effective when administered to an animal with a microbial infection. These polymers are clearly described as being useful as additives or applied to the surface of an object to impart antibacterial properties to the surface of the object. The '102 patent discloses that the polymers can be included as an additive in a surface coating, such as paint, lacquer or varnish. (*Id.*, at col. 30, lines 18-22.) Additionally, the '102 patent discloses that the polymers can be incorporated into or attached to the surface of an object such as a catheter, a contact lens, a medical device, or woven or nonwoven fabric. (*Id.*, at col. 30, lines 23-39.) It is my opinion these disclosures in the '102 patent would suggest to a person of ordinary skill in the art that the disclosed polymers are to be used as an additive or are to be included in an object to prevent or slow microbial growth and do not provide any motivation to administer the polymers in a pharmaceutical composition as a therapeutic agent to an animal infected with a microbial infection. A person of ordinary skill in the art is aware that a polymer that is to be used as an additive or that is to be attached to an object is not necessarily effective or safe as a therapeutic agent. For example, catheters have been impregnated with silver, but silver is not administered as a therapeutic agent. Additionally, the '102 patent is silent with respect to the route by which one of the disclosed polymers would be administered to an animal. The '102 patent does not describe any carriers or diluents which are compatible with the polymers and which may be used to formulate a

pharmaceutical composition. Therefore, a person of ordinary skill in the art would not necessarily expect a polymer shown to function as an antimicrobial agent when attached to or incorporated into an object to be effective in treating a microbial infection in an animal. Thus, it is my opinion that a person of ordinary skill in the art, based upon the disclosures of the '102 patent, would not have been motivated to treat a microbial infection in an animal by administering an effective amount of a pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application.

9. Second, a person of ordinary skill in the art would not necessarily expect the polymers described in the '102 patent to be effective when administered to an animal with a microbial infection simply because an *in vitro* assay showed the polymers inhibit bacterial growth. The '102 patent discloses the anti-microbial activity of the polymers were tested *in vitro* using mammalian cells. The '102 patent further discloses an *in vitro* assay conducted to determine the toxicity of these polymers on mammalian cells. The '102 patent is silent as to whether the polymers tested are effective and safe *in vivo*. A person of ordinary skill in the art is aware that the *in vitro* assays disclosed in the '102 patent do not necessarily indicate whether the compound would be effective *in vivo*. A person of ordinary skill in the art is also aware there are examples of compounds that have been shown to be effective *in vitro*, but have not been effective *in vivo*. Therefore, a person of ordinary skill in the art would not necessarily expect a polymer shown to have antimicrobial activity *in vitro* to be effective to treat an animal with a microbial infection when administered as a pharmaceutical composition. Thus, it is my opinion that a person of ordinary skill in the art, based upon the disclosures of the '102 patent, would not have been motivated to treat a microbial infection in an animal by administering an effective amount of a

pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application.

10. Third, a person of ordinary skill in the art would not necessarily expect the polymers described in the '102 patent to be effective when administered to an animal with a microbial infection simply because the polymers were tested for toxicity to birds, fish and mammals. New antibacterial materials to be employed as surface coatings need to act as antibacterial agents while not having adverse consequences to the surrounding environment. A person of ordinary skill in the art would read the disclosure in the '102 patent regarding the reduced toxicity of the polymers to birds, fish and mammals as being related to toxicity studies, such as those required by the U.S. Environmental Protection Agency ("EPA"). The '102 patent discloses the polymers attached to an object may leach into the environment from the surface of the object. (*Id.*, at col. 4, lines 60-65.) Because the polymers may eventually leach from the object, the EPA may require a showing the polymers are not toxic to humans. *See* "Guidelines for Exposure Assessment," Risk Assessment Forum, U.S. Environmental Protection Agency (May 1992), pages 2 & 5 (Exhibit A2). As such, it is my opinion the toxicity studies described in the '102 patent are studies to be conducted to satisfy EPA standards. It is my opinion that just because the '102 patent discloses the polymers are not toxic under EPA standards does not suggest to a person of ordinary skill in the art that the polymers are necessarily safe and effective for administration to animals. Therefore, a person of ordinary skill in the art would not necessarily expect that a polymer to be used as an additive or applied to the surface of an object and having acceptable toxicity to necessarily be safe and effective when administered to an animal. Thus, it is my opinion that a person of ordinary skill in the art, based upon the disclosures of the '102 patent, would not have been motivated to treat a microbial infection in an animal by administering an effective amount of

a pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application.

11. For at least the reasons described above, it is my opinion that a person of ordinary skill in the art, based upon the disclosures of the '102 patent, would not have been motivated to treat a microbial infection in an animal by administering an effective amount of a pharmaceutical composition containing an oligomer of a specific structure and a pharmaceutically acceptable carrier or diluent, as claimed in the patent application.

12. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the present patent application or any patent issued thereon.

Respectfully submitted,

David P. Nicolau, Pharm.D., FCCP

Date: 6/25/08

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Curriculum Vitae

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RESIDENCE

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ACADEMIC EDUCATION

1982 - 1987 Bachelor of Science in Pharmacy
Northeastern University
Boston, Massachusetts

1988 - 1990 Doctor of Pharmacy
Medical University of South Carolina
Charleston, South Carolina

POSTGRADUATE TRAINING and EDUCATION

1987 - 1988 ASHP Residency in Hospital Pharmacy
The University Hospital
Boston University Medical Center
Boston, Massachusetts

1990 - 1991 ASHP Clinical Pharmacy Residency
Adult Internal Medicine
Medical University Hospital
Medical University of South Carolina
Charleston, South Carolina

1991 - 1993 Clinical Pharmacy Fellowship
Infectious Diseases Pharmacotherapy
Hartford Hospital
Hartford, Connecticut

David P. Nicolau, PharmD, FCCP

PROFESSIONAL EXPERIENCE

October 2005 – present Hartford Hospital, Hartford, Connecticut
Director, Center for Anti-Infective Research and Development

October 2002 – 2005 Hartford Hospital, Hartford, Connecticut
Co-Director, Center for Anti-Infective Research and Development

July 1993 - present Hartford Hospital, Hartford, Connecticut
Coordinator for Research, Departments of Medicine,
Division of Infectious Diseases and Pharmacy
Committee Activity - Antibiotic Subcommittee; Institutional Animal Care and Use Committee; Cancer Program Task Force

January 1990 - June 1991 Roper Hospital, Charleston, South Carolina
Co-Director, Clinical Pharmacokinetic Service

October 1988 - June 1991 Roper Hospital, Charleston, South Carolina
Staff Pharmacist (Part-time)

July 1987 - August 1988 The University Hospital, Boston, Massachusetts
Staff Pharmacist (Part-time)

June 1987 - August 1988 The Children's Hospital, Boston, Massachusetts
Staff Pharmacist (Part-time)

Pharmacy License Massachusetts (#20244) Connecticut (#7728)

RESEARCH EXPERIENCE

Preclinical Development (*in vivo* models)**:** Extensive experience with a variety of animal models including: endocarditis, osteomyelitis, intra-abdominal sepsis, thigh infection, and pneumonia and related PK/PD assessments. Function as principal investigator many industry sponsored studies. **Phase I** (healthy subject)**:** Responsible for the development, implementation, management of studies conducted in our 24 bed clinical research center. Studies primarily designed to assess the pharmacokinetic and/or pharmacodynamic profiles. Functioned as principal investigator on both hospital and industry sponsored projects and principal on Investigational New Drug (IND) applications with FDA. **Phase II - IV** (Clinical)**:** Responsible for the development, implementation, management of clinical studies involving antimicrobials conducted within our institution. Studies have included the assessment of drug disposition and effectiveness in a variety of patient populations. Functioned as principal investigator for and industry sponsored INDs, as well as, sponsor for IND studies. Within these broad research areas experience has also been acquired with various analytical (e.g., HPLC, microbiologic assay) and microbiology based techniques. In my present position, I am responsible for the fiscal, administrative and scientific course of the Center for Anti-Infective Research & Development.

David P. Nicolau, PharmD, FCCP

PUBLICATIONS

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12. **Nicolau DP**, Quintiliani R, Nightingale CH. Once-Daily Aminoglycosides. *Connecticut Medicine* 1992;56:561-563. *Errata*: 1992;56:652.

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69. Klepser ME, Zhu Z, **Nicolau DP**, Banevicius MA, Ross JW, Broisman L, Belliveau PP, Quintiliani R, Nightingale CH. Oral Absorption of Trimethoprim/Sulfamethoxazole in Patients with AIDS. *Pharmacotherapy* 1996;16:656-662.

70. Lacy MK, Hitt CM, Nightingale CH, Quintiliani R, **Nicolau DP**. The Pharmacoeconomic Benefits of Once-Daily Aminoglycoside Dosing. *Drug Benefit Trends* 1996;8:36-39.

PUBLICATIONS (con't)

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73. **Nicolau DP**, Nightingale CH, Quintiliani R. Continuous Infusion Beta-Lactams: A Pharmacodynamic Approach. *Infectious Diseases in Clinical Practice* 1996;5:432-434.

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22a. Belliveau PP, **Nicolau DP**, Nightingale CH, Quintiliani R. Once-daily gentamicin: Experience with 118 patients with postpartum endometriosis (Abstract No. 114). American College of Clinical Pharmacy, Annual Meeting, St. Louis, Missouri, July-August 1994

23a. **Nicolau DP**, Crowe H, Nightingale CH, Quintiliani R. Bioavailability of fluconazole administered via a feeding tube in intensive care unit patients (Abstract No. 115). American College of Clinical Pharmacy, Annual Meeting, St. Louis, Missouri, July-August 1994

24a. Marangos MN, **Nicolau DP**, Nightingale CH, Quintiliani R. Influence of aspirin on the treatment of experimental *Enterococcus faecalis* endocarditis (Abstract No. 7). Connecticut Infectious Diseases Society, 10th Annual Meeting, Southbury, Connecticut, September 1994

25a. Patel KB, Belliveau PP, Nightingale CH, **Nicolau DP**, Quintiliani R. Absorption of ciprofloxacin in febrile and afebrile patients (Abstract No. 8). Connecticut Infectious Diseases Society, 10th Annual Meeting, Southbury, Connecticut, September 1994

26a. Patel KB, Marangos MN, **Nicolau DP**, Nightingale CH. Synergistic activity of vancomycin or teicoplanin combined with streptomycin against VanB-type resistant enterococci with variable levels of Vm-resistance (Abstract No. 2). Connecticut Infectious Diseases Society, 10th Annual Meeting, Southbury, Connecticut, September 1994

ABSTRACTS (con't)

27a. **Nicolau DP**, Marangos MN, Nightingale CH, Quintiliani R Jr., Courvalin P, Quintiliani R. Efficacy of vancomycin and teicoplanin alone and in combination with streptomycin in experimental VanB-type resistant enterococcal endocarditis (Abstract No. 1). Connecticut Infectious Diseases Society, 10th Annual Meeting, Southbury, Connecticut, September 1994

28a. **Nicolau DP**, Nightingale CH, Tessier PR, Fu Q, Xuan D, Esguerra EM, Quintiliani R. The effect of fleroxacin and ciprofloxacin on the pharmacokinetics of multiple-dose caffeine (Abstract No. 57). 5th International Symposium on New Quinolones, Singapore, August 1994

29a. Marangos MN, Onyeji CO, **Nicolau DP**, Nightingale CH. Aspirin disposition in rabbits (Abstract No. P45). American Association for Laboratory Animal Science, 45th Annual Meeting, Pittsburgh, Pennsylvania, October 1994

30a. Patel KB, Marangos MN, **Nicolau DP**, Nightingale CH. Synergistic activity of vancomycin (Vm) or teicoplanin (Te) combined with streptomycin (Sm) against VanB-type resistant enterococci with variable levels of Vm-resistance (Abstract No. E100). American Society for Microbiology, 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994

31a. Patel KB, Belliveau PP, Nightingale CH, **Nicolau DP**, Quintiliani R. Absorption of ciprofloxacin in febrile and afebrile patients (Abstract No. A39). American Society for Microbiology, 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994

32a. Onyeji CO, Nightingale CH, Tessier PR, **Nicolau DP**, Bow LM. Activities of clarithromycin, azithromycin and ofloxacin in combination with liposomal or unencapsulated GM-CSF against intramacrophage *Mycobacterium avium-i*ntracellulare (Abstract No. E138). American Society for Microbiology, 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994

33a. **Nicolau DP**, Marangos MN, Nightingale CH, Quintiliani R Jr., Courvalin P, Quintiliani R. Efficacy of vancomycin (Vm) and teicoplanin (Te) alone and in combination with streptomycin (Sm) in experimental enterococcal endocarditis (Abstract No. B73). American Society for Microbiology, 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994

ABSTRACTS (con't)

34a. **Nicolau DP**, Nightingale CH, Banevicius MA, Fu Q, Quintiliani R. Ceftazidime serum bactericidal activity: Continuous infusion versus intermittent injections (Abstract No. A90). American Society for Microbiology, 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida, October 1994

35a. Nightingale CH, Belliveau PP, **Nicolau DP**, Quintiliani R. Streamlining antibiotic therapy in the hospital setting/cost containment by switching from parenteral to oral therapy (Abstract No. Is-100). 4th Western Pacific Congress of Chemotherapy and Infectious Diseases, Manila, Philippines, December 1994

36a. Hitt CM, Patel KB, **Nicolau DP**, Nightingale CH. Effects of piperacillin/tazobactam on once-daily gentamicin pharmacokinetics (Abstract No. P-437E). American Society of Hospital Pharmacists, 29th Annual Midyear Clinical Meeting, Miami, Florida, December 1994

37a. Klepser ME, Patel KB, **Nicolau DP**, Quintiliani R, Nightingale CH. Comparative activities of ofloxacin and ciprofloxacin combined with ceftazidime and piperacillin against *Pseudomonas aeruginosa*. The Role of Quinolones in Hospital Pharmacy, Poster symposium presented during American Society of Hospital Pharmacists, 29th Annual Midyear Clinical Meeting, Miami, Florida, December 1994

38a. **Nicolau DP**, Ross JW, Nightingale CH, Quintiliani R. Influence of gender on treatment outcomes and pharmacoeconomics of *Pneumocystis carinii* pneumonia (PCP) in patients with AIDS (Abstract No. 299). Second National Conference on Human Retroviruses and Related Infections, Washington, D.C., January-February 1995

39a. **Nicolau DP**, Nightingale CH, Quintiliani R. Influence of gender on the pharmacokinetic interaction of fleroxacin and ciprofloxacin with caffeine (Abstract No. 68). American College of Clinical Pharmacy, Winter Practice and Research Forum, Orlando, Florida, February 1995

40a. **Nicolau DP**, Klepser ME, Banevicius MA, Nightingale CH, Quintiliani R. Serum bactericidal activity of ceftazidime continuous infusion and intermittent dosing combined with once-daily gentamicin or ciprofloxacin (Abstract No. 42). American College of Clinical Pharmacy, Winter Practice and Research Forum, Orlando, Florida, February 1995

ABSTRACTS (con't)

41a. Marangos MN, Skoutelis AT, Zhu Z, **Nicolau DP**, Bassaris H, Quintiliani R, Nightingale CH. Absorption of ciprofloxacin in patients with diabetic gastroenteropathy (Abstract No. 416). 7th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, March 1995

42a. Xuan D, **Nicolau DP**, DeVivo J, Tessier PR, Bow L, Quintiliani R, Nightingale CH. Endotoxin concentration reduction with the addition of 5S-IgG immunoglobulin in the presence of cefotaxime (Abstract No. 1290). 7th European Congress of Clinical Microbiology and Infectious Diseases, Vienna, Austria, March 1995

43a. Banevicius MA, Epp E, Nightingale CH, **Nicolau DP**. Influence of Oxyrase on the microdilution susceptibility testing of *B. fragilis* to five antimicrobials (Abstract No. C362). American Society for Microbiology, 95th General Meeting, Washington, D.C., May 1995

44a. Klepser ME, Patel KB, **Nicolau DP**, Quintiliani R, Nightingale CH. Comparative activities of ofloxacin and ciprofloxacin combined with ceftazidime and piperacillin against *Pseudomonas* (Abstract No. 3053). 19th International Congress of Chemotherapy, Montreal, Canada, July 1995

45a. Marangos MN, **Nicolau DP**, Nightingale CH, Quintiliani R. Influence of aspirin on the treatment of experimental *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* endocarditis (Abstract No. 3054). 19th International Congress of Chemotherapy, Montreal, Canada, July 1995

46a. **Nicolau DP**, Nightingale CH, Tessier PR, Fu Q, Xuan D, Esguerra EM, Quintiliani R. Effect of fleroxacin and ciprofloxacin on the pharmacokinetics of caffeine (Abstract No. 3273). 19th International Congress of Chemotherapy, Montreal, Canada, July 1995

47a. Nightingale CH, **Nicolau DP**, Quintiliani R. Pharmacodynamics of aminoglycosides. Satellite Symposium on the Pharmacodynamics of Antimicrobials, Presented during the 19th International Congress of Chemotherapy, Montreal, Canada, July 1995

48a. Klepser ME, Zhu Z, **Nicolau DP**, Banevicius MA, Ross JW, Broisman L, Belliveau PP, Quintiliani R, Nightingale CH. Characterization of oral absorption for trimethoprim/ sulfamethoxazole (160mg/800mg) in patients with AIDS (Abstract No. 115). American College of Clinical Pharmacy, Annual Meeting, Washington, D.C., August 1995

ABSTRACTS (con't)

49a. Patel KB, **Nicolau DP**, Nightingale CH, Quintiliani R. Comparative serum bactericidal activity of ceftizoxime and cefotaxime against intermediate penicillin-resistant Streptococcus pneumoniae (Abstract No. A87). American Society for Microbiology, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 1995

50a. Hitt CM, Klepser ME, Nightingale CH, Quintiliani R, **Nicolau DP**. Pharmacoeconomic impact of a once-daily aminoglycoside program (Abstract No. N18). American Society for Microbiology, 35th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 1995

51a. Alkhal AM, Crowe HM, **Nicolau D**, Nightingale C, Quintiliani R. Once-daily aminoglycoside use in patients with Gram-positive endocarditis (Abstract No. 174). Infectious Diseases Society of America, San Francisco, California, September 1995

52a. **Nicolau DP**, Feng YJ, Wu AHB, Bernstein S, Nightingale CH. Swine model for the evaluation of drug clearance via a novel dialysis system (Abstract No. P39). American Association for Laboratory Animal Science, 46th Annual Meeting, Baltimore, Maryland, October 1995

53a. Berstein SP, **Nicolau DP**, Wu AHB, Feng YJ, Nightingale CH. CAVH for myoglobin clearance in swine. American Society of Nephrology, 28th Annual Meeting, November 1995

54a. Dempsey CL, **Nicolau DP**, Wagley W, Shillington AC, Jewell MA, Farley PA. Disease state management model for pneumonia: a multi-center benchmark project (Abstract No. P-281E). American Society of Health-Systems Pharmacists, 30th Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 1995

55a. Nodoushani M, **Nicolau DP**, Hitt CH, Quintiliani R, Nightingale CH. Analysis of Nephrotoxicity Associated with Once-Daily Aminoglycoside Administration (Abstract No. P-521E). American Society of Health-Systems Pharmacists, 30th Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 1995

56a. Udeh E, **Nicolau DP**, Chow MSS, Nightingale CH, Quintiliani R. Assessment of a Drug Usage Evaluation Program on Serum Aminoglycoside Concentrations in Patients Receiving Once-Daily Aminoglycosides (Abstract No. P-251E). American Society of Health-Systems Pharmacists, 30th Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 1995

ABSTRACTS (con't)

57a. Marangos MN, Klepser ME, **Nicolau DP**, Nightingale CH, Quintiliani R. *In Vivo* Effect of Azithromycin Subinhibitory Concentrations on the Mortality of Experimental *P. aeruginosa* sepsis (Abstract No. 9.06). Third International Conference on the Macrolides Azalides and Streptogramins, Lisbon, Portugal, January 1996

58a. Klepser ME, **Nicolau DP**, Quintiliani R, Nightingale CH. Comparison of the Bactericidal Activity of Clindamycin Administered Every Eight and Twelve Hours Against *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Bacteroides fragilis* (Abstract No. 74). American College of Clinical Pharmacy, Annual Meeting, Nashville, Tennessee, August 1996

59a. Owens RC, Patel KB, Nightingale CH, Quintiliani R, Banevicius MA, **Nicolau DP**. Oral Bioavailability of Ciprofloxacin in Patients with AIDS (Abstract No. A008). American Society for Microbiology, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, September 1996

60a. Hitt CM, Nightingale CH, Quintiliani R, **Nicolau DP**. Cost Analysis of Single Dose Ceftriaxone Versus Continuous Infusion Cefotaxime (Abstract No. N09). American Society for Microbiology, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, September 1996

61a. Xuan D, **Nicolau DP**, Tessier PR, Bow L, Quintiliani R, Nightingale CH. Effectiveness of 5S-IgG Immunoglobulin on Experimental Gram-Negative Sepsis (Abstract No. G079). American Society for Microbiology, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, September 1996

62a. Marangos MN, **Nicolau DP**, Nightingale CH, Quintiliani R. Influence of Gentamicin Dosing Interval on the Efficacy of Penicillin Containing Regimens in Experimental *Enterococcal faecalis* Endocarditis (Abstract No. B03). American Society for Microbiology, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, September 1996

63a. Nie L, **Nicolau DP**, Tessier PR, Kourea HP, Browner BD, Nightingale CH. Use of a Ofloxacin Bioabsorbable Composite for the Treatment of Experimental *Pseudomonas aeruginosa* Osteomyelitis (Abstract No. A076). American Society for Microbiology, 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, Louisiana, September 1996

ABSTRACTS (con't)

64a. Owens RC, Patel KB, Nightingale CH, Quintiliani R, Banevicius MA, **Nicolau DP**. Oral Bioavailability of Ciprofloxacin in Patients with AIDS. Connecticut Infectious Diseases Society, 12th Annual Meeting, Southbury, Connecticut, September 1996

65a. **Nicolau DP**, Banevicius MA, Marangos MN, Klepser ME, Nightingale CH, Quintiliani R. Influence of Adjunct Azithromycin Therapy on the Mortality of Experimental Sepsis due to *Pseudomonas aeruginosa* (Abstract No. 225). 10th Mediterranean Congress of Chemotherapy, Antalya, Turkey, October 1996

66a. **Nicolau DP**, Tessier PR, Nightingale CH, Quintiliani R. Beneficial Effect of Ticlopidine Administration in Experimental *S. aureus* Endocarditis (Abstract No. 222). 10th Mediterranean Congress of Chemotherapy, Antalya, Turkey, October 1996

67a. Lacy MK, Lu W, Xu X, Tessier PR, **Nicolau DP**, Quintiliani R, Nightingale CH. Comparison of the Bactericidal Characteristics of Levofloxacin and Ciprofloxacin against *Streptococcus pneumoniae* in an *In Vitro* Model of Infection. The Role of Quinolones in Hospital Pharmacy, Poster symposium presented during American Society of Hospital Pharmacists, 31st Annual Midyear Clinical Meeting, New Orleans, Louisiana, December 1996

68a. Owens RC Jr., Banevicius MA, **Nicolau DP**, Nightingale CH, Quintiliani R. Evaluation of *In-Vtro* Synergy Between Tobramycin and Selected Beta-Lactams (Abstract No. A-151). American Society for Microbiology, 97th General Meeting, Miami Beach, Florida, May 1997

69a. **Nicolau DP**. Pharmacokinetic, Pharmacodynamic and Efficacy Considerations in Oral Cephalosporin Therapy Selection (Abstract No. S34). The Role of New Cephalosporins in Rational Antimicrobial Therapy. 8th European Congress of Clinical Microbiology and Infectious Diseases, Lausanne, Switzerland, May 1997

70a. **Nicolau DP**, Tessier PR, Quintiliani R, Nightingale CH. Assessment of *In Vitro* Synergy Between Trovafloxacin and Ceftriaxone or Vancomycin Against *S. pneumoniae* (Abstract No. 2249). 20th International Congress of Chemotherapy, Sydney, Australia, June-July 1997

ABSTRACTS (con't)

71a. **Nicolau DP**, Loeser SE, Lacy MK, Quintiliani R, Nightingale CH. Pharmacokinetics of Continuous and Intermittent Ceftazidime in ICU Patients with Nosocomial Pneumonia (Abstract No. 4252). 20th International Congress of Chemotherapy, Sydney, Australia, June-July 1997

72a. Lacy MK, Lu W, Xu X, Tessier PR, **Nicolau DP**, Quintiliani R, Nightingale CH. Pharmacodynamic Comparison of Levofloxacin and Ciprofloxacin Against *S. pneumoniae* in an *In Vitro* Model (Abstract No. 3278). 20th International Congress of Chemotherapy, Sydney, Australia, June-July 1997

73a. Lacy MK, Banevicius MA, Tessier PR, Nightingale CH, Quintiliani R, **Nicolau DP**. Evaluation of the Efficacy of Trovafloxacin and Ciprofloxacin against *S. pneumoniae* in a Sepsis Model (Abstract No. 2250). 20th International Congress of Chemotherapy, Sydney, Australia, June-July 1997

74a. Owens RC Jr., **Nicolau DP**, Quintiliani R, Nightingale CH. Bactericidal Activity of Clarithromycin, Azithromycin and Cefuroxime against PCN-S, -I, -R Pneumococci (Abstract No. 3202). 20th International Congress of Chemotherapy, Sydney, Australia, June-July 1997

75a. Owens RC Jr., Keung CF, Gardner S, Eller MG, Weir SJ, **Nicolau DP**, Nightingale CH. Pharmacokinetic and Food Effect Evaluation of Rifapentine in Subjects Seropositive for the Human Immunodeficiency Virus (Abstract No. A-2). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

76a. Lacy MK, **Nicolau DP**, Banevicius MA, Nightingale CH, Quintiliani R. Protective Effect of Trovafloxacin, and Ampicillin Against Isolates of *S. pneumoniae* with Varying Penicillin Susceptibilities (Abstract No. B-097). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

77a. Lacy MK, Owens RC Jr., Xu X, **Nicolau DP**, Quintiliani R, Nightingale CH. A Comparison of Bactericidal Activity after Multidose Administration of Clarithromycin, Azithromycin, and Cefuroxime Axetil against *S. pneumoniae* (Abstract No. A-43). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

ABSTRACTS (con't)

78a. **Nicolau DP**, Tessier PR, Quintiliani R, Nightingale CH. Synergistic Activity of Trovafloxacin and Ceftriaxone or Vancomycin Against *S. pneumoniae* with Variable Penicillin Susceptibilities (Abstract No. E-63). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

79a. Ambrose PG, Quintiliani R, Nightingale CH, **Nicolau DP**. Evaluation of Continuous Infusion Cefuroxime in the Therapy of Community-Acquired Pneumonia (Abstract No. K-4). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

80a. Lacy M, **Nicolau DP**, Nightingale CH, Geffken A, Teng R, Vincent J, Quintiliani R. The Pharmacokinetics of Trovafloxacin in Patients with AIDS (Abstract No. A-64). 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, Canada, September 28-October 1, 1997

81a. Ambrose PG, Quintiliani R, Nightingale CH, **Nicolau DP**. Evaluation of Continuous Infusion Cefuroxime in the Therapy of Community-Acquired Pneumonia. (Abstract No. 76). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

82a. Lacy M, **Nicolau DP**, Nightingale CH, Geffken A, Teng R, Vincent J, Quintiliani R. The Pharmacokinetics of Trovafloxacin in Patients with AIDS (Abstract No. 92E). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

83a. Klepser ME, Patel KB, **Nicolau DP**, Quintiliani R, Nightingale CH. Comparison of the Bactericidal Activity of Intermittent and Continuous Infusion Vancomycin Dosing Regimens against Methicillin-Resistant *S. aureus* and *E. faecalis* (Abstract No. 72). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

84a. Owens RC Jr., Tessier PR, Ambrose PG, Lacy MK, Quintiliani R, Nightingale CH, **Nicolau DP**. Bactericidal Activities of Ceftriaxone i.m., Ceftriaxone i.v. and Cefixime p.o. Against Typical Community Acquired Tract (TCART) Pathogens (Abstract No. 73). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

ABSTRACTS (con't)

85a. Owens RC Jr., Banevicius MA, **Nicolau DP**, Nightingale CH, Quintiliani R. Evaluation of *In-Vtro* Synergy between Tobramycin and Selected Beta-Lactam Agents (Abstract No. 81E). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

86a. Owens RC Jr., Keung CF, Gardner S, Eller MG, Weir SJ, **Nicolau DP**, Nightingale CH. Pharmacokinetic and Food Effect Evaluation of Rifapentine in Subjects Seropositive for the Human Immunodeficiency Virus (Abstract No. 188E). 1997 Annual Meeting, American College of Clinical Pharmacy, Phoenix, Arizona, November 9-12, 1997

87a. Lacy MK, Owens RC Jr., Xu X, **Nicolau DP**, Quintiliani R, Nightingale CH. A Comparison of Bactericidal Activity after Single and Multidose Administration of Clarithromycin, Azithromycin, and Cefuroxime Axetil against *S. pneumoniae* (Abstract No. 10.07). Fourth International Conference on the Macrolides, Azalides, Streptogramins and Ketolides. Barcelona, Spain, January 1998

88a. Lacy M, **Nicolau DP**, Nightingale CH, Geffken A, Teng R, Vincent J, Quintiliani R. The Pharmacokinetics of Trovafloxacin in Patients with AIDS (Abstract No. T-119). 2nd European Congress of Chemotherapy and 7th Biennial Conference on Antiinfective Agents and Chemotherapy, Hamburg, Germany, May 10-13, 1998.

89a. **Nicolau DP**, Lacy MK, McNabb JC, Quintiliani R, Nightingale CH. Continuous versus Intermittent Administration of Ceftazidime in Intensive Care Unit Patients with Nosocomial Pneumonia (Abstract No. K-107). 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 24-27, 1998

90a. Xuan D, **Nicolau DP**, Bow L, Quintiliani R, Nightingale CH. *In Vitro* Reduction of Endotoxin Induction of TNF-α in Human Monocyte-enriched Peripheral Blood Mononuclear cells with the 5S Fragment of Immunoglobulin G (Abstract No. G-040). 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 24-27, 1998

91a. McNabb JC, Lacy MK, Ross JW, Rousseau, Nightingale CH, **Nicolau DP**. Randomized, Cross-Over Adherence Trial of Azithromycin and Clarithromycin for MAC Prophylaxis in AIDS Patients (Abstract No. I-142). 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 24-27, 1998

ABSTRACTS (con't)

92a. Lacy M, Tessier PR, **Nicolau DP**, Nightingale CH, Quintiliani R. Comparison of Vancomycin Pharmacodynamics Against Methicillin-Resistant Staphylococcus Isolates with 1 Gram Every 12 or 24 Hour Dosing (Abstract No. 63). 1998 Annual Meeting, American College of Clinical Pharmacy, Cincinnati, Ohio, November 8-11, 1998

93a. Bui KQ, McNabb JC, Li C, Nightingale CH, **Nicolau DP**. Mononuclear and Polymorphonuclear Leukocyte Disposition of Clarithromycin (CLARI) and Azithromycin (AZI) in AIDS Patients Requiring *Mycobacterium avium complex* (MAC) Prophylaxis (Abstract No. 255-Sa). 36th Annual Meeting of the Infectious Diseases Society of America, Denver, Colorado, November 12-15, 1998

94a. Ambrose PG, Richerson MA, Bui K, Stanton B, **Nicolau DP**, Nightingale CH, Quintiliani R. A Cost-Effectiveness Analysis of Cefepime (PIM) versus Ceftazidime (TAZ) in Intensive Care Unit (ICU) Patients with Hospital-Acquired Pneumonia (HAP) (Abstract No. 666-Fr). 36th Annual Meeting of the Infectious Diseases Society of America, Denver, Colorado, November 12-15, 1998

95a. McNabb JC, Xuan D, Owens RC Jr., Quintiliani R, Nightingale CH, **Nicolau DP**. Comparison of Azithromycin Leukocyte Disposition in Healthy Volunteers versus Volunteers with AIDS (Abstract No. B 41). Second International Meeting on the Therapy of Infections, Florence, Italy, November 18-21, 1998

96a. Bui KQ, McNabb JC, LI CH, Nightingale CH, **Nicolau DP**. Mononuclear and Polymorphonuclear Leukocyte Disposition of Clarithromycin and Azithromycin in AIDS Patients Requiring *Mycobacterium avium complex* Prophylaxis (Abstract No. 74E). International Congress on Clinical Pharmacy, Orlando, Florida, April 11-14, 1999

97a. McNabb JC, Xuan D, Owens RC Jr., Quintiliani R, Nightingale CH, **Nicolau DP**. Comparison of Azithromycin Leukocyte Disposition in Healthy Volunteers versus Volunteers with AIDS (Abstract No. 73E). International Congress on Clinical Pharmacy, Orlando, Florida, April 11-14, 1999

98a. **Nicolau DP**, Onyeji CO, Zhong M, Tessier PR, Banevicius MA, Nightingale CH. *In Vivo* Efficacy of Cefprozil against *Streptococcus pneumoniae* Using the Pharmacokinetic Profile in Children (Abstract No. 1777). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

ABSTRACTS (con't)

99a. Lu J, Xuan D, **Nicolau DP,** Nightingale CH. Population Pharmacokinetic study of Tobramycin after Once-daily dosing in Hospitalized Patients (Abstract No. 1008). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

100a. Xuan D, **Nicolau DP,** Bow L, Quintiliani R, Nightingale CH. Investigation of the Kinetic Profile of Endotoxin-Mediated TNF-α Induction in a Rat Endotoxin Septic Shock Model (Abstract No. 0264). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

101a. Bui KQ, Banevicius MA, Nightingale CH, Quintiliani R, **Nicolau DP**. *In Vitro* and *In Vivo* Influence of Adjunct Clarithromycin on the Treatment of Mucoid *Pseudomonas aeruginosa* (Abstract No. G-0786). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

102a. Bui KQ, Ambrose PG, Grant EM, Nightingale CH, **Nicolau DP,** Quintiliani R. Pharmacokinetics and Pharmacoeconomic Evaluation of Ticarcillin-Clavulanate Administered either as Continuous or Intermittent Infusion with Once-Daily Gentamicin (Abstract No. A-1192). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

103a. **Nicolau DP**, Banevicius MA, Nightingale CH, Quintiliani R. Beneficial Effect of Adjunctive Azithromycin in the Treatment of Mucoid *Pseudomonas aeruginosa* Pneumonia (Abstract No. 787). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

104a. McNabb JC, Nightingale CH, Quintiliani R, **Nicolau DP**. Analysis of the Cost-Effectiveness of Ceftazidime in Nosocomial Pneumonia given as a Continuous Infusion vs. Intermittent Infusion (Abstract No. 1864). 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, California, September 26-29, 1999

105a. Bui KQ, Banevicius MA, Nightingale CH, Quintiliani R, **Nicolau DP**. *In Vitro* and *In Vivo* Influence of Adjunct Clarithromycin on the Treatment of Mucoid *Pseudomonas aeruginosa* (Abstract 91E). Annual Meeting American College of Clinical Pharmacy, Kansas City, Missouri, October 24-27, 1999

ABSTRACTS (con't)

106a. Bui KQ, Ambrose PG, Grant EM, Nightingale CH, **Nicolau DP,** Quintiliani R. Pharmacokinetics and Pharmacoeconomic Evaluation of Ticarcillin-Clavulanate Administered either as Continuous or Intermittent Infusion with Once-Daily Gentamicin (Abstract 91E). Annual Meeting American College of Clinical Pharmacy, Kansas City, Missouri, October 24-27, 1999

107a. Xuan D, **Nicolau D**, Nightingale C. Population Pharmacokinetic Study of Gentamicin after Once-Daily Dosing in Hospitalized Patients (Abstract No. 3411). American Association of Pharmaceutical Scientists Annual Meeting, New Orleans, Louisiana, November 14-18, 1999

108a. Bui KQ, Ambrose PG, **Nicolau DP**, Lapin CD, Nightingale CH, Quintiliani R. Steady-State Pharmacokinetics of High Dose Meropenem in Adult Cystic Fibrosis Patients (Abstract 15). 1999 Annual Meeting of Infectious Diseases Society of America, November 18-21, 1999

109a. McNabb JC, Quintiliani R, Nightingale CH, **Nicolau DP**. Comparison of the Bactericidal Activity of Trovafloxacin and Ciprofloxacin alone and in combination with Cefepime against *P. aeruginosa* (Abstract 100363). 1999 Annual Meeting of Infectious Diseases Society of America, November 18-21, 1999

110a. Grant EM, Zhong MK, **Nicolau DP**, Quintiliani R, Fitzgerald J, Nightingale CH. Determination of Potential and Extent of Drug-Drug Interaction of Oral Levofloxacin and Oxycodone (Abstract 100692). 1999 Annual Meeting of Infectious Diseases Society of America, November 18-21, 1999

111a. Grant EM, Ambrose PG, Quintiliani R, **Nicolau DP**, Nightingale CH. Stability of Intravenous Meropenem Solution in a Portable Refrigerated Infusion Pump (Abstract 5). 1999 Annual Meeting of Infectious Diseases Society of America, November 18-21, 1999

112a. Bui KQ, Banevicius MA, Nightingale CH, Quintiliani R, **Nicolau DP**. *In Vitro* and *In Vivo* Influence of Adjunct Clarithromycin on the Treatment of Mucoid *Pseudomonas aeruginosa* (Abstract 11.15). 5th International Conference on the Macrolides, Azalides, Streptogramins, Ketolides & Oxazolidinones, Seville, Spain, January 26-28, 2000

113a. **Nicolau DP**, Banevicius MA, Nightingale CH, Quintiliani R. Beneficial Effect of Adjunctive Azithromycin in the Treatment of Mucoid *Pseudomonas aeruginosa* Pneumonia (Abstract No. 11.16). 5th International Conference on the Macrolides, Azalides, Streptogramins, Ketolides & Oxazolidinones, Seville, Spain, January 26-28, 2000

ABSTRACTS (con't)

114a. McNabb JC, Ross J, Abriola K, Nightingale CH, Turley C, **Nicolau DP**. Adherence to HAART by MEMS predicts virologic outcome in minority/IVDU clinic population (Abstract No. TuOrB416), World AIDS Conference, Durban, South Africa, July 9, 2000

115a. **Nicolau DP**, Mattoes HM, Banevicius MA, Xuan D, Nightingale CH. Pharmacodynamic profile of a novel des-F(6) quinolone, BMS-284756, against *Streptococcus pneumoniae* in the neutropenic thigh infection model (Abstract No. 290), 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

116a. Xuan D, Zhong MK, Mattoes HM, Bui KQ, **Nicolau DP**, Quintiliani R, Nightingale CH. *Streptococcus pneumoniae* Response to Repeated Exposure of Moxifloxacin or Levofloxacin Using a Rabbit Tissue Cage Model (Abstract No. 286). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

117a. Grant EM, Ambrose PG, **Nicolau DP**, Nightingale CH, Quintiliani R. Clinical Efficacy of Cefepime in Pneumonia Caused by *Pseudomonas aeruginosa* (Abstract No. 742). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

118a. Grant EM, **Nicolau DP**, Nightingale CH, Quintiliani R. Influence of Oxycodone on the Bioavailability of Gatifloxacin (Abstract No. 2272). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

119a. Kim MK, Zhou W, Tessier PR, Xuan D, Nightingale CH, **Nicolau DP**. Bacterial Kill of ABT-773 in a Murine Pneumococcal Pneumonia Model (Abstract No. 1019). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

120a. Kim MK, Xuan D, Quintiliani R, Nightingale CH, **Nicolau DP**. Pharmacokinetic and Pharmacodynamic Profile of High Dose Extended Interval Piperacillin/Tazobactam (Abstract No. 2249). 40th Interscience Conference on Antimicrobial Agents and Chemotherapy, Toronto, Canada, September 17-20, 2000

121a. **Nicolau DP**, Onyeji CO, Banevicius MA, Li J, Nightingale CH. Effects of Adjunctive Treatment with Combined Cytokines in a Neutropenic Mouse Model of Multidrug-Resistant *Enterococcus faecalis* Septicemia (Abstract 322). Annual Meeting American College of Clinical Pharmacy, Los Angeles, California, November 6, 2000

ABSTRACTS (con't)

122a. Mattoes HM, Banevicius MA, Li D, Turley C, Xuan D, Nightingale CH, **Nicolau DP**. Pharmacodynamic Assessment of Gatifloxacin Against *Streptococcus pneumoniae*. 16th Annual Meeting, Connecticut Infectious Diseases Society, Southbury, Connecticut October 2000

123a. Kim MK, Xuan D, Quintiliani R, Nightingale CH, **Nicolau DP**. Pharmacokinetic and Pharmacodynamic Profile of High Dose Extended Interval Piperacillin/Tazobactam. 16th Annual Meeting, Connecticut Infectious Diseases Society, Southbury, Connecticut October 2000

124a. Kuti JL, Grant EM, **Nicolau DP**, Nightingale CH, Quintiliani R. Clinical Efficacy and Pharmacoeconomics of Piperacillin/Tazobactam Administered by Continuous versus Intermittent Infusion (Abstract RP-323). American Society of Health-System Pharmacists, 35th Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 2000

125a. Kim MK, Zhou W, Tessier PR, Xuan D, Nightingale CH, **Nicolau DP**. Bacterial Kill of ABT-773 in a Murine Pneumococcal Pneumonia Model (Abstract No. P9.015). 22nd International Congress of Chemotherapy, Amsterdam, The Netherlands, June 30 – July 3, 2001

126a. Mattoes HM, Capitano B, Kim MK, Xuan D, Quintiliani R, Nightingale CH, **Nicolau DP**. Comparative Pharmacokinetic and Pharmacodynamic Profile of Piperacillin/Tazobactam 3.375g q4h and 4.5g q6h (Abstract No. 950). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

127a. Kim MK, Banevicius MA, Zhong M, Nightingale CH, **Nicolau DP**. Clearance of Quinupristin-Dalfopristin (Synercid®) And Their Main Metabolites during Continuous Veno-Venous Hemofiltration (CVVH) With or Without Dialysis (Abstract No. 935). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

128a. Kuti JL, Le TN, Nightingale CH, **Nicolau DP**, Quintiliani R. Pharmacoeconomic Impact of a Pharmacist-Managed Automatic Intravenous (IV) to Oral (PO) Conversion Program (Abstract No. 391). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

129a. Capitano B, Leshem AO, Nightingale CH, **Nicolau DP**. Influence of Methicillin-Resistance on the Cost of Infection Management due to *Staphylococcus Aureus* in a Long-Term Care Facility (Abstract No. 397). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

ABSTRACTS (con't)

130a. Xuan D, Banevicius MA, Capitano B, Kim MK, Nightingale CH, **Nicolau DP**. Pharmacodynamic Assessment of Ertapenem (MK-0826) against *Streptococcus pneumoniae* in the Murine Neutropenic Thigh Infection Model (Abstract No. 2097). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

131a. Xuan D, Ye M, Nightingale CH, **Nicolau DP**. Pharmacokinetics of ABT-773, a New Semi-synthetic Ketolide in Neutropenic Lung-infected Mice: A Population Approach (Abstract No. 2185). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

132a. Mattoes HM, Tessier PR, Nightingale CH, **Nicolau DP**. Bactericidal Activity of Telithromycin against Macrolide Resistant (*erm*(B), *mef*(A)), and Fluoroquinolone Resistant *Streptococcus pneumoniae* in a Murine Thigh Infection Model (Abstract No. 1656). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

133a. Simpson IN, Di Modugno E, Jabes D, **Nicolau D**. Oxapenem AM-112: In vivo efficacy alone and in combination with ceftazidime in animal models of infection, involving pathogens producing Class A and Class C β–lactamases (Abstract No. F-385). 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 22-25, 2001

134a. Kuti JL, Grant EM, **Nicolau DP**, Nightingale CH, Quintiliani R. Clinical Efficacy and Pharmacoeconomics of Piperacillin/Tazobactam Administered by Continuous versus Intermittent Infusion (Abstract 139E). Annual Meeting American College of Clinical Pharmacy, Tampa, Florida, October 21-24, 2001

135a. Kuti JL, Le TN, Nightingale CH, **Nicolau DP**, Quintiliani R. Pharmacoeconomic Impact of a Pharmacist-Managed Automatic Intravenous to Oral Conversion Program (Abstract No. 290E). Annual Meeting American College of Clinical Pharmacy, Tampa, Florida, October 21-24, 2001

136a. Kuti JL, Nightingale CH, Quintiliani R, **Nicolau DP**. Pharmacodynamic Profile of Continuously Infused Piperacillin/Tazobactam against *Pseudomonas aeruginosa* using Monte Carlo Analysis (Abstract No. 229E). Annual Meeting American College of Clinical Pharmacy, Tampa, Florida, October 21-24, 2001

ABSTRACTS (con't)

137a. Capitano B, Leshem AO, Nightingale CH, **Nicolau DP**. Influence of Methicillin-Resistance on the Cost of Infection Management due to *Staphylococcus Aureus* in a Long-Term Care Facility (Abstract No. 185E). Annual Meeting American College of Clinical Pharmacy, Tampa, Florida, October 21-24, 2001

138a. Xuan D, Ye M, Nightingale CH, **Nicolau DP**. Pharmacokinetics of ABT-773, a New Semi-synthetic Ketolide in Neutropenic Lung-infected Mice: A Population Approach (Abstract No. 5.04). International Conference on Macrolides, Azalides, Streptogramins, Ketolides and Oxazolidinones (ICMAS-KO) VI, Bologna, Italy, January 2002

139a. Kim MK, Zhou W, Tessier PR, Xuan D, Nightingale CH, **Nicolau DP**. Bacterial Kill of ABT-773 in a Murine Pneumococcal Pneumonia Model (Abstract No. 5.05). International Conference on Macrolides, Azalides, Streptogramins, Ketolides and Oxazolidinones (ICMAS-KO) VI, Bologna, Italy, January 2002

140a. Hariprasad SM, Mieler WF, Schwartz SG, Barrow D, Sun XK, **Nicolau DP**, Holz ER. Vitreous Penetration of Orally Administered Gatifloxacin in Humans (Abstract No. **XX**). Association for Research in Vision and Ophthalmology, Fort Lauderdale, Florida May 5 - 10, 2002

141a. **Nicolau DP**, Simpson IN, Urch JC. Oxapenem XOB (AM-114): In vitro activity alone and in combination with amoxycillin or cefaclor against community-acquired respiratory tract pathogens (Abstract No. 222). 12th European Congress of Clinical Microbiology and Infectious Disease, Milan, Italy, April 24-27, 2002

142a. Zervos MJ, Hershberger E, **Nicolau DP**, Ritchie D, Blackner L, Coyle EA, Donnelly AJ, Eckel SF, Eng RHK, Hiltz A, Kuyumjian AG, McDaniel A, Hogan P, Lubowski TJ. Impact of Fluoroquinolone Usage on Pathogen Susceptibility: A 10 year multicenter Evaluation (Abstract No. A-7). 102nd General Meeting of the American Society of Microbiology, Salt Lake City, Utah, May 2002

143a. Capitano B, Mattoes HM, Shore E, O'Brien A, Braman S, Nightingale CH, **Nicolau DP**. Bonchopulmonary Pharmacokinetic Profile of Moxifloxacin in Older Adults Undergoing Diagnostic Bronchoscopy (Abstract No. P2681). European Respiratory Society Annual Congress, Stockholm, Sweden, September 14-18, 2002

144a. Capitano B, Maglio D, Banevicius MA, Nightingale CH, **Nicolau DP**. Bactericidal Effects of Cethromycin (ABT-773) in an Immunocompetent Murine Pneumococcal Pneumonia Model (Abstract No. A1-1271). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 29, 2002

ABSTRACTS (con't)

145a. Dandekar PK, Maglio D, Sutherland CA, Nightingale CH, **Nicolau DP**. Pharmacokinetics of Meropenem 0.5g and 2g Every 8h Administered as a 3h Infusion (Abstract No. A1-1388). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 29, 2002

146a. Kuti JL, Dandekar PK, Nightingale CH, **Nicolau DP**. Pharmacodynamic (PD) Comparison of Prolonged and Traditional Infusions of Meropenem (MEM) in Gram-Negative Bacteria (Abstract No. A1-637). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 28, 2002

147a. Dandekar PK, Tessier PR, Williams P, Nightingale CH, **Nicolau DP**. Pharmacodynamic Profile of Daptomycin Against *E. faecalis* and Methicillin Resistant *S. aureus* in a Murine Thigh Infection Model (Abstract No. A1-1270). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 29, 2002

148a. Kuti JL, Kotapati S, Williams P, Capitano B, Nightingale CH, **Nicolau DP**. Pharmacoeconomic Analysis of Amphotericin B Lipid Complex (ABLC) versus Liposomal Amphotericin B (L-AmB) in the Treatment of Fungal Infections (Abstract No. O-1000). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 28, 2002

149a. Li C, **Nicolau DP**, Lister P, Quintiliani R, Nightingale CH. Pharmacodynamic Study of β–lactams alone and in Combination with β–lactamase Inhibitors against β–lactamase Inducible *Pseudomonas aeruginosa* Infections (Abstract No. A1-1255). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 29, 2002

150a. Simpson IN, Urch CJ, Jabes D, Candiani **G, Nicolau DP.** AM-114: Chemistry and biological activity of a novel orally absorbed broad-spectrum oxapenem β-lactamase inhibitor. (Abstract No. P1003). 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, California, September 29, 2002

151a. Kuti JL, Florea NR, Nightingale CH, **Nicolau DP**. Pharmacodynamics (PD) of Meropenem (MEM) and Imipenem (IMI) against Enterobacteriaceae and *Pseudomonas aeruginosa* (PSA) (Abstract No. 100319). 40th Annual Meeting of the Infectious Diseases Society of America, Chicago, Illinois, October 24-27, 2002

ABSTRACTS (con't)

152a. Zervos M, Hershberger E, **Nicolau D**, Ritchie D, Blackner L, Coyle E, Donnelly A, Eckel S, Eng R, Hiltz A, Kuymjian A, McDaniel A, Hogan P, Lubowski T. A 10 Year Multicenter Study of the Association Between Quinolone (Q) Susceptibility and Quinolone Density Rate (QDR) Using Baseline to Endpoint (BE) and Trend-line Analyses (TL) (Abstract No. 101028). 40th Annual Meeting of the Infectious Diseases Society of America, Chicago, Illinois, October 24-27, 2002

153a. Dandekar PK, Tessier PR, Williams P, Nightingale CH, **Nicolau DP**. Pharmacodynamic Profile of Daptomycin Against *E. faecalis* and Methicillin Resistant *S. aureus* in a Murine Thigh Infection Model (Abstract No. 156E). 2002 Annual Meeting American College of Clinical Pharmacy, Albuquerque, New Mexico, October 20-23, 2002

154a. Maglio D, Nightingale CH, **Nicolau DP**. Cantharidin-induced Inflammatory Blister Technique: Focus on Healing and Blister Resolution (Abstract No. 257E). 2002 Annual Meeting American College of Clinical Pharmacy, Albuquerque, New Mexico, October 20-23, 2002

155a. Maglio D, **Nicolau DP**, Teng R, Thyrum PT. Penetration of Meropenem (MEM) into Human Skin Blister Fluid (Abstract No. 155E). 2002 Annual Meeting American College of Clinical Pharmacy, Albuquerque, New Mexico, October 20-23, 2002

156a. Li C, **Nicolau DP**, Lister P, Quintiliani R, Nightingale CH. Simultaneous Determination of Ticarcillin and Clavulanate in Rabbit Serum and Tissue Cage Fluid (TCF) by HPLC (Abstract No. W4013). American Association of Pharmaceutical Scientists, 2002 Annual Meeting & Exposition, Toronto, Ontario, Canada, November 10-14, 2002

157a. Capitano B, Mattoes H, Shore E, O'Brien A, Braman S, Sutherland C, Nightingale C, **Nicolau D**. Intrapulmonary Disposition of Multiple Dose Moxifloxacin, Levofloxacin and Azithromycin in Older Adults (Abstract No. 4234). 2003 American Thoracic Society International Conference, Seattle, Washington, May 13-16, 2003.

158a. Kuti JL, Nightingale CH, Knauft RF, **Nicolau DP**. Pharmacokinetics of Continuously Infused Meropenem in Adults with Cystic Fibrosis (Abstract No. 2135). 2003 American Thoracic Society International Conference, Seattle, Washington, May 13-16, 2003.

159a. O'Riordan TG, Chugtai BI, **Nicolau D**, Palmer LB. Gatifloxacin Levels in Airway Secretions of Patients with Ventilator-Associated Tracheobronchitis (Abstract No. p 368). 2003 American Thoracic Society International Conference, Seattle, Washington, May 13-16, 2003.

ABSTRACTS (con't)

160a. Florea NR, Kuti JL, Nightingale CH, **Nicolau DP**. Prevalence and Characteristics of Intravenous to Oral Conversion Programs for Anti-Infectives in the United States (Abstract No. 197). 2003 Spring Practice and Research Forum of the American College of Clinical Pharmacy, Palm Springs, California, April 29, 2003.

161a. LI C, **Nicolau DP**, Nightingale CH. Simultaneous Pharmacokinetic Modeling of Piperacillin and Tazobactam Concentrations in Rabbit Serum and Tissue Cage Fluid (Abstract No. 124). 2003 Spring Practice and Research Forum of the American College of Clinical Pharmacy, Palm Springs, California, April 29, 2003.

162a. **Nicolau DP**, Tessier PR, Rubinstein I, Nightingale CH. In Vivo Immunomodulatory Profile of Telithromycin in a Murine Infection Model (Abstract No. P1620). 13th European Congress of Clinical Microbiology and Infectious Diseases. Glasgow, Scotland, May 13, 2003.

163a. Dandekar PK, Williams P, Tessier PR, Farrell DJ, Nightingale CH, **Nicolau DP**. *In vivo* Efficacy of Telithromycin against *S. Pneumoniae* with Ribosomal Mutations (Abstract No. A-304). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14, 2003

164a. Dandekar PK, Williams P, Tessier PR, Farrell DJ, Nightingale CH, **Nicolau DP**. Assessment of Telithromycin against *S. Pneumoniae* with Ribosomal Mutations Using Time-Kill Methodology (Abstract No. E-1525). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 16, 2003

165a. Dandekar PK, Tessier PR, Williams P, Zhang C, Nightingale CH, **Nicolau DP**. Determination of the Pharmacodynamic Profile of Daptomycin against *S. pneumoniae* with Varying Susceptibility to Penicillin in a Murine Thigh Infection Model (Abstract No. A-311). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14, 2003

166a. Fetterly GJ, Ong C, Bhavnani SM, Loutit J, Porter S, Ambrose PG, **Nicolau DP**. Characterization of Pharmacokinetics (PK) of Oritavancin (ORI) in Plasma and Blister Fluid in Normal Healthy Volunteers (Abstract No. A-18). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14, 2003

ABSTRACTS (con't)

167a. Maglio D, Ong C, Banevicius MA, Nightingale CH, **Nicolau DP**. Lack of Impact of Extended Spectrum Beta-lactamases (ESBL) on the *in vivo* Pharmacodynamics (PD) of Cefepime (FEP) (Abstract No. A-1317). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 16, 2003

168a. Li C, **Nicolau DP**, Lister L, Quintiliani R, Nightingale CH. *In vivo and in vitro* Induction of AmpC β–lactamase by Clavulanate (Abstract No. C1-667). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 15, 2003

169a. Florea NR, Tessier PR, Zhang C, Nightingale CH, **Nicolau DP**. Bronchopulmonary Pharmacodynamics of Moxifloxacin (MFX) and Levofloxacin (LEV) Against *Streptococcus pneumoniae* (SPN) Using An *In-Vitro* Model (Abstract No. A-1162). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 15, 2003

170a. Kuti JL, Nightingale CH, **Nicolau DP**. Evaluation of Pharmacodynamic Target Attainment between Healthy Subject and patient Data using Monte Carlo Simulation (Abstract No. A-9). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14, 2003

171a. Kuti JL, Nightingale CH, **Nicolau DP**. Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram (OPTAMA) – North America (NA) 2002 (Abstract No. A-7). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 14, 2003

172a. KotapatiS, Kuti JL, Nightingale CH, **Nicolau DP**. Clinical and Economic Outcomes of a Meropenem (MEM) Dosing Protocol Based on Pharmacodynamic (PD) Concepts (Abstract No. A-1364). 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, Illinois, September 16, 2003

173a. Zhang C, Nightingale CH, **Nicolau DP**. Reverse Phase High Performance Liquid Chromatographic Method for Determination of Moxifloxacin in special growth media. 6th Drug Analysis Conference, Chinese Pharmaceutical Journal and SHINADZU Cup Meeting, Peking, China, September 2003

174a. **Nicolau DP**, Jenkins SG. Resistance phenotypes and multi-drug resistance among isolates of *Streptococcus pneumoniae* from the USA during PROTEKT US Year 2 (2001-2002) (Abstract No. 203). 41st Annual Meeting Infectious Diseases Society of America, San Diego, California, October 10, 2003

ABSTRACTS (con't)

175a. Babalola CP, Nightingale CH, **Nicolau DP**. Influence of Granulocyte Colony–Stimulating Factor (G-CSF) on treatment of *Pseudomonas aeruginosa* Pneumonia in Non-Neutropenic Host (Abstract No. 104). 2003 Annual Meeting American College of Clinical Pharmacy, Atlanta, Georgia, November 2-5, 2003

176a. Ong CT, Tessier P, Li C, Nightingale CH, **Nicolau DP**. In Vivo Pharmacodynamic Characterization of Meropenem and its Impact on the Selection of Resistance Among Pseudomonas aeruginosa (Abstract No. 105). 2003 Annual Meeting American College of Clinical Pharmacy, Atlanta, Georgia, November 2-5, 2003

177a. KotapatiS, Kuti JL, Nightingale CH, **Nicolau DP**. Clinical and Economic Outcomes of a Meropenem Dosing Protocol Based on Pharmacodynamic Concepts (Abstract No. 102E). 2003 Annual Meeting American College of Clinical Pharmacy, Atlanta, Georgia, November 2-5, 2003

178a. Kiffer CRV, Mendes C, Kuti JL, Nicolau DP. Optimizing Pharmacodynamic Target Attainment Using the Mystic Antibiogram (OPTAMA) – South America 2002 (Poster IH 101). Congresso Brasileiro de Microbiologia, Florianópolis - Santa Catarina – Brazil, November 17-20, 2003.

179a. Iannini PB, Nicolau DP, Zitt MJ. Start Treatment with Appropriate Antibiotic Respiratory Therapy: An Expert Panel Discussion (Abstract No. 1018). Annual Meeting of the American Academy of Allergy, Asthma & Immunology, San Francisco, California, March 2004

180a. Ong CT, Dandekar PK, Sutherland CA, Nightingale CH, **Nicolau DP**. Bronchopulmonary Pharmacokinetics of Telithromycin: Implications for Activity against *Streptococcus pneumoniae* (Abstract No. 3567, E19). 2004 American Thoracic Society International Conference, Orlando, Florida, May 23-24, 2004.

181a. Brown S, **Nicolau D**, Patel M. Multi-drug resistance among isolates of *Streptococcus pneumoniae* from respiratory and blood culture sources in the US: Data from PROTEKT US Year 2 (2001-2002) (Abstract No. A46, E9). 2004 American Thoracic Society International Conference, Orlando, Florida, May 23-24, 2004.

ABSTRACTS (con't)

182a. Masterton RG, Kuti JL, Turner PJ, **Nicolau DP**. Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram (OPTAMA) – *Escherichia coli* (EC) and *Klebsiella pneumoniae* (KP) in Europe, 2002 (Abstract No. P1105). 14th European Congress of Clinical Microbiology and Infectious Disease, Prague, Czech Republic, May 1-4, 2004.

183a. Masterton RG, Kuti JL, Turner PJ, **Nicolau DP**. Optimizing Pharmacodynamic Target Attainment using the MYSTIC Antibiogram (OPTAMA) – *Acinetobacter* sp. (*AS*) and *P. aeruginosa* (*PSA*) in Europe, 2002 (Abstract No. P1104). 14th European Congress of Clinical Microbiology and Infectious Disease, Prague, Czech Republic, May 1-4, 2004.

184a. Ong CT Kuti JL, **Nicolau DP**. Pharmacodynamic Analysis of Imipenem-Cilastatin, Meropenem, and Piperacillin-Tazobactam for Empiric Therapy in Surgical Wound Infections - A Report from the OPTAMA Program (Abstract No. SE215). 90th Annual Clinical Congress of American College of Surgeons, New Orleans, Louisiana, October 10-14, 2004.

185a. Kotapati S, Kuti JL, **Nicolau DP**. Pharmacodynamic Comparison of β-lactam Antibiotics for the Empiric Treatment of Secondary Peritonitis - A Report from the OPTAMA Program (Abstract No. SE167). 90th Annual Clinical Congress of American College of Surgeons, New Orleans, Louisiana, October 10-14, 2004.

186a. Kuti JL, **Nicolau DP**. Pharmacodynamics of meropenem in patients receiving continuous venovenous hemofiltration (CVVH): a report from the 2003 OPTAMA Program (Abstract No. 316). Infectious Diseases Society of America, Boston, MA, September 30-October 3, 2004.

187a. Ellis JM, Kuti JL, **Nicolau DP**. Pharmacodynamics of antimicrobials against *Streptococcus pneumoniae* in pediatric patients: a report from the OPTAMA Program (Abstract No. 314). Infectious Diseases Society of America, Boston, MA, September 30-October 3, 2004.

188a. Ellis JM, Kuti JL, **Nicolau DP**. Pharmacodynamics of antimicrobials against Gram-negative bacteria in pediatric patients: a report from the OPTAMA Program (Abstract No. 315). Infectious Diseases Society of America, Boston, MA, September 30-October 3, 2004.

ABSTRACTS (con't)

189a. Sun HK, Kuti JL, Nightingale CH, **Nicolau DP**. Pharmacodynamics of RO4908463 (CS-023) for the Empiric Treatment of Nosocomial Pneumonia Program (Abstract No. 320). Infectious Diseases Society of America, Boston, MA, September 30-October 3, 2004.

190a. Kotapati S, Kuti JL, Nightingale CH, **Nicolau DP**. Clinical (CR) and Microbiological Response (MR) of Different Antibiotic Classes on Extended Spectrum β-lactamase (ESBL) Producing Pathogens in a Large Teaching Center (Abstract No. 443). Infectious Diseases Society of America, Boston, MA, September 30-October 3, 2004.

191a. Ellis JM, Kuti JL, **Nicolau DP**. Pharmacodynamics of antimicrobials against Gram-negative bacteria in pediatric patients: a report from the OPTAMA Program (Abstract No. 266E). American College of Clinical Pharmacy, 2004 Annual Meeting, Dallas, TX, October 24-27, 2004

192a. Li C, Kuti JL, Nightingale CH, Mansfield DL, Dana A, **Nicolau DP**. Population Pharmacokinetics of Continuous and Intermittent Infusion Piperacillin/Tazobactam in Patients with Complicated Intra-abdominal Infection (Abstract No. 375). World Conference - Dosing of Anti-Infectives, Nürnberg, Germany, September 9-11, 2004

193a. Li C, Sutherland C, Nightingale CH, **Nicolau DP**. HPLC Determination of Tigecycline in Human Samples (Abstract No. 376b). World Conference - Dosing of Anti-Infectives, Nürnberg, Germany, September 9-11, 2004

194a. Ong CT, Tessier PR, Li C, Nightingale CH, **Nicolau DP**. Efflux pumps in *Pseudomonas aeruginosa* do not translate to in vivo failure in Efficacy or emergence of resistance to meropenem, imipenem, or cefepime (Abstract No. A-1867). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

195a. Grillot AL, Stamos D, Grossman T, Bi Y, Carver M, Deininger D, Drumm J, Fowlie A, Gross C, Letiran A, Liao Y, Ma J, Mani N, Moore J, **Nicolau D**, Olson E, Parsons J, Partaledis J, Perola E, Ronkin S, Tang Q, Tian SK, Tessier P, Wang T, Wei Y, Zhang H, Charifson P. A New Class of Dual Targeting Inhibitors of GyrB and ParE (Abstract No. F-1951). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

ABSTRACTS (con't)

196a. Maglio D, Banevicius MA, Sutherland C, Babalola C, Nightingale CH, **Nicolau DP**. *In Vivo* Pharmacodynamics of Ertapenem Against Gram-negative Pathogens (Abstract No. A-1868). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

197a. Maglio D, Sun HK, Patel T, Banevicius MA, Nightingale CH, **Nicolau DP**, Arya A, Wang G, Phan LT. Pharmacodynamics of a New Ketolide EP-13420 in a Murine *S. pneumoniae* (SPN) Pneumonia Model (Abstract No. F-1407). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

198a. Kotapati S, Kuti JL, Nightingale CH, **Nicolau DP**. Clinical and Microbiologic Response of Extended Spectrum β-lactamase Producing Klebsiella sp. And Escherichia coli Infections Treated with Cefepime (Abstract No. A-1590). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

199a. Sun HK, Ong CT, Umer A, Harper D, Troy S, Nightingale CH, **Nicolau DP**. Pharmacokinetic Profile of Tigecycline in Serum and Blister Fluid After Multiple Intravenous Administrations in Healthy Adults (Abstract No. A-12). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

200a. Kuti JL, Nightingale CH, **Nicolau DP**. Pharmacodynamics of CS-023 against *Staphylococcus aureus* and *Pseudomonas aeruginosa* (Abstract No. A-141). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

201a. Ong CT, Babalola C, Nightingale CH, **Nicolau DP** Penetration, Intracellular Accumulation, and Efflux of Tigecycline in Human Polymorphonuclear Neutrophils (Abstract No. A-1303). 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington D.C., October 30 – November 2, 2004

202a. Sun HK, Kuti JL, **Nicolau DP**. Pharmacodynamics of Antimicrobials for the Empiric Treatment of Nosocomial Pneumonia: A Report from the OPTAMA Program (Abstract No. P902). 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2-5, 2005

ABSTRACTS (con't)

203a. Kuti JL, Ong C, Lo M, Melnick D, Soto N, **Nicolau DP**. Comparison of Pharmacodynamic Target Attainment (TA) Calculated by Monte Carlo Simulation with Microbiological Response (MR) for Two Carbapenems in the Treatment of Complicated Skin and Skin Structure Infections (Abstract No. O122). 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2-5, 2005

204a. Ludwig E, Maglio D, Konkoly-Thege M, Kuti J, **Nicolau D**. Pharmacodynamic comparison of intravenous antimicrobials against Pseudomonas aeruginosa in Hungarian hospitals - A report from the OPTAMA Program (Abstract No. P904). 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2-5, 2005

205a. Jones ME, **Nicolau DP**, Kuti JL, Nightingale C, Draghi DC, Flamm RK, Sahm DF. Activity and pharmacodynamics of RO490-8463 (CS-023), a carbapenem with activity against MRSA (Abstract No. P1573). 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2-5, 2005

206a. Duchin K, Sun H, Shaw JP, **Nicolau D**. Pharmacokinetics and Tissue Penetration of Telavancin in Healthy Volunteers (Abstract No. P898). 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2-5, 2005

207a. Ellis JM, Kuti JL, **Nicolau DP**. Pharmacodynamics of Meropenem (MER) and Cefotaxime (CTX) for Pediatric Meningitis – A Report from the OPTAMA Program (Abstract No. 513). Pediatric Academic Societies' Annual Meeting, Washington, DC, May 14–17, 2005

208a. **Nicolau DP**, Sutherland CA, Arguedas A, Dagan R, Pichichero ME. Pharmacokinetics of Cefprozil in Plasma and Middle Ear Fluid (MEF) of Children Undergoing Treatment for Acute Otitis Media (AOM) (Abstract No. A-17). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

209a. Lau W, Mercer D, Itani K, **Nicolau DP**, Kuti JL, Mansfield D, Dana A. A Randomized Comparative Study of Piperacillin/Tazobactam (TZP) Continuous (CI) vs. Intermittent Infusion (II) for Complicated Intra-Abdominal Infection (Abstract No. L-581). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

210a. Lee SY, Kotapati S, Kuti JL, Nightingale CH, **Nicolau DP**. Impact of Extended Spectrum β-Lactamase (ESBL) Producing Bacteria on Hospital Cost: a Case Control Study (Abstract No. O-174). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

ABSTRACTS (con't)

211a. Lee SY, Kotapati S, Kuti JL, Nightingale CH, **Nicolau DP**. Impact of Extended Spectrum β-Lactamase (ESBL) Producing Bacteria on Initial Antibiotic Therapy: A Case Controlled Study (Abstract No. K-1290). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

212a. Lee SY, Tessier PR, Murphy CK, **Nicolau DP**. Bactericidal Efficacy of ABI-0043, a Novel Rifamycin, in a Murine Pneumococcal Pneumonia Model (Abstract No. F-2044). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

213a. DeRyke CA, Xu D, **Nicolau DP**. Evaluation of Bacterial Kill when Modeling the Bronchopulmonary Pharmacokinetic Profile of Moxifloxacin (MOX) and Levofloxacin (LVX) against *parC* Containing Isolates of *S. pneumoniae* (SPN) (Abstract No. A-453). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

214a. Sun HK, Du X, DeRyke CA, Doern GV, **Nicolau DP**. Simulated Bronchopulmonary Concentrations of Moxifloxacin (MOX) and Levofloxacin (LVX) against *ParE* Containing Isolates of *S. Pneumoniae* (SPN) (Abstract No. A-454). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

215a. Li C, Du X, Kuti JL, **Nicolau DP**. Clinical Pharmacodynamics (PD) of Meropenem (MEM) in Adult Patients with Lower Respiratory Tract Infections (LRTI) (Abstract No. A-1147). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

216a. Lee SY, Kuti JL, **Nicolau DP**. Cefepime Pharmacodynamics in Patients with ESBL and non-ESBL Infections (Abstract No. A-1151). 45th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, December 2005

217a. DeRyke CA, Xu D, **Nicolau DP**. Evaluation of Bacterial Kill when Modeling the Bronchopulmonary Pharmacokinetic Profile of Moxifloxacin (MOX) and Levofloxacin (LVX) against *parC* Containing Isolates of *S. pneumoniae* (SPN) (Abstract No. 185E). American College of Clinical Pharmacy, 2005 Annual Meeting, San Francisco, CA, October 23-26, 2005

218a. Sun HK, **Nicolau DP**, Kuti JL. Resource Utilization and Outcomes of Adults Admitted to a Tertiary Hospital with Community Acquired Pneumonia (CAP) Caused by *Streptococcus pneumoniae* (SP) (Abstract No. 271). American College of Clinical Pharmacy, 2005 Annual Meeting, San Francisco, CA, October 23-26, 2005

ABSTRACTS (con't)

219a. Lee SY, Kotapati S, Kuti JL, Nightingale CH, **Nicolau DP**. Impact of Extended Spectrum β-Lactamase (ESBL) Producing Bacteria on Initial Antibiotic Therapy: A Case Controlled Study (SP) (Abstract No. 274E). American College of Clinical Pharmacy, 2005 Annual Meeting, San Francisco, CA, October 23-26, 2005

220a. DeRyke CA, Kuti JL, Mansfield D, Dana A, **Nicolau DP**. Pharmacoeconomics of Continuous versus Intermittent Infusion Piperacillin/tazobactam for the Treatment of Hospitalized Patients with Complicated Intra-abdominal Infection (Abstract No. RP76). American Society of Hospital Pharmacists, 40th Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 2005

221a. Kiffer CRV, Mendes C, Eagye KJ, Kuti JL, **Nicolau DP**. Pharmacodynamic comparison of three carbapenems against extended spectrum Beta-lactamase (ESBL) producing *Escherichia coli* and *Klebsiella* spp from the MYSTIC Program in Brazil. (Abstract No. P1550). 16TH European Congress of Clinical Microbiology and Infectious Diseases, Nice, France, April 2006

222a. Stein GE, Schooley S, **Nicolau DP**. Urinary Bactericidal Activity of Levofloxacin (750mg) against Fluoroquinolone-Resistant Uropathogens. (Abstract No. P1533). 16TH European Congress of Clinical Microbiology and Infectious Diseases, Nice, France, April 2006

223a. Wong SL, Shaw JP, **Nicolau DP**, Barrierre S, Kitt M, Goldberg M. Pharmacokinetic Modeling of Telavancin Penetration into Skin Blister Fluid (Abstract No. A2786). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

224a. Zhanel GG, Baudry TJ, Laing M, Decorby M, Nored A, **Nicolau DP**, Pharmacodynamic Activity of Tigecycline vs. Molecularly Characterized Multi-Drug Resistant Extended Spectrum β-lactamase (ESBL) producing *E. coli* Using an In Vitro Model. (Abstract No. A1679). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

225a. Deryke CA, Fan HW, Banevicius MA, **Nicolau DP**. *In Vivo* Efficacy of Human Simulated Exposures of Ertapenem (ERT) and Meropenem (MEM) against Extended-Spectrum Beta-Lactamase (ESBL) producing *Klebsiella pneumoniae* (KP) and *Escherichia coli* (EC). (Abstract No. A0011). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

ABSTRACTS (con't)

226a. Deryke CA, **Nicolau DP**. Is All Time Above the Minimum Inhibitory Concentration (MIC) the Same: Implications for In Vivo Modeling. (Abstract No. A0005). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

227a. Eagye KJ, Shore E, Dobkin E, Palter M, **Nicolau DP**, Kuti JL. Differing Epidemiology and Resistance Patterns of Respiratory Isolates (RI) from Three Intensive Care Units (ICUs) within the Same Institution. (Abstract No. K0259). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

228a. Eagye KJ, **Nicolau DP**, Kuti JL. Impact of Superinfection (SI) on Hospital Length of Stay (LOS) and Costs in Patients with Ventilator-Associated Pneumonia (VAP). (Abstract No. K0286). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

229a. **Nicolau DP**, Sutherland C, Winget D, Baughman RP. Bronchopulmonary Pharmacokinetics of Levofloxacin 750 mg Once-daily in Patients with Acute Exacerbation of Chronic Bronchitis. (Abstract No. A0332). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

230a. Deryke CA, Kuti JL, **Nicolau DP**. Is Re-evaluation of Current Susceptibility Breakpoints for Gram-Negative Rods (GNR) Based on Pharmacodynamic (PD) Assessment. (Abstract No. D0703). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

231a. Banevicius MA, Deryke CA, Kaplan N, Vaughn D, **Nicolau DP**. In Vivo Pharmacodynamic Profiling of API-1252 Against *Staphylococcus aureus* in a Murine Thigh Model. (Abstract No. D0703). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

232a. Deryke CA, Sutherland C, Zhang B, **Nicolau DP**, Kuti JL. Pharmacokinetics (PK) and Serum Bactericidal Activity of High-Dose Daptomycin (DAP) with and without Co-Administration of Gentamicin Against Isolates of *Staphylococcus aureus* and *Enterococcus* species. (Abstract No. A0629). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

ABSTRACTS (con't)

233a. Deryke CA, Kuti JL, **Nicolau DP**. Pharmacodynamic (PD) Target Attainment (TA) as a Surrogate Marker for Antibiotic Efficacy in Cost-Effectiveness Analyses (CEA). (Abstract No. O1465). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

234a. Tessier PR, Fan HW, Tanaka SK, **Nicolau DP**. Pharmacokinetic/Pharmacodynamic Profile of PTK0796 against *S. pneumoniae* in a Murine Pneumonia Model). (Abstract No. F1-1973). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 27-30, 2006

235a. Kuti JL, Dowzicky M, **Nicolau DP**. A Pharmacodynamic (PD) Model to Assess Tigecycline (TG) Predicted Efficacy Compared with Other Antibiotics for Hospital-Acquired Pneumonia (HAP). (Abstract No. 213) 44th Annual Meeting of Infectious Diseases Society of America, Toronto, Canada, October 12-15, 2006

236a. Kuti JL, Dowzicky M, **Nicolau DP**. Pharmacodynamic (PD) Performance of Tigecycline (TG) Compared with Other Antibiotics for Complicated Skin and Soft Tissue Infections (SSTI). (Abstract No. P1-020). 10th Western Pacific Congress on Chemotherapy and Infectious Diseases, Fukuoka International Congress Center, Fukuoka, Japan, December 3-6, 2006

237a. Lee SY, Fan HW, **Nicolau DP**. Antibacterial Effects of Moxifloxacin and Levofloxacin Simulating Epithelial Lining Fluid Concentrations against Community-Acquired Methicillin-Resistant Staphylococcus Aureus (CA-MRSA). (Abstract No. P2-027). 10th Western Pacific Congress on Chemotherapy and Infectious Diseases, Fukuoka International Congress center, Fukuoka, Japan, December 3-6, 2006

238a. Kiffer C, Kuti J, Mendes C, Sinto S, Koga P, **Nicolau D**. Pharmacodynamic comparison of linezolid, teicoplanin, and vancomycin against clinical isolates of Staphylococcus aureus and coagulase negative staphylococci collected from hospitals in Brazil. (Abstract No. P1375). 17th European Congress of Clinical Microbiology and Infectious Diseases - 25th International Congress of Chemotherapy, Munich, Germany, March 31 – April 3, 2007

239a. Banevicius MA, Kaplan N, Vaughan D, **Nicolau DP**. Comparative Dose Studies of API-1252 and Linezolid Against Hospital-Acquired (HA) and Community-Acquired (CA) Methicillin-Resistant *Staphylococcus aureus* (MRSA) in a Murine Thigh Model. (Abstract No. O455). 17th European Congress of Clinical Microbiology and Infectious Diseases - 25th International Congress of Chemotherapy, Munich, Germany, March 31 – April 3, 2007

ABSTRACTS (con't)

240a. Eagye KJ, Nicolau DP, Heilmann K, Quinn J, Doern GV, Gallagher G, Abramson M. A pharmacodynamic analysis of resistance trends in pathogens from patients with infection in intensive care units in the United States between 1993 and 2004. (Abstract No. P1813). 17th European Congress of Clinical Microbiology and Infectious Diseases - 25th International Congress of Chemotherapy, Munich, Germany, March 31 – April 3, 2007

241a. Eagye KJ, Kuti JL, Dowzicky M, **Nicolau DP**. Pharmacodynamic Evaluation of 7 Antibiotics Recommended for Secondary Peritonitis, including the novel agent Tigecycline using Global Resistance Data. (Abstract No. O421). 17th European Congress of Clinical Microbiology and Infectious Diseases - 25th International Congress of Chemotherapy, Munich, Germany, March 31 – April 3, 2007

242a. Kim A, Sutherland C, Kuti JL, **Nicolau DP**. Optimal Piperacillin/Tazobactam Dosing against *Pseudomonas aeruginosa*: Prolonged or Continuous Infusion? (Abstract No. P1372). 17th European Congress of Clinical Microbiology and Infectious Diseases - 25th International Congress of Chemotherapy, Munich, Germany, March 31 – April 3, 2007

243a. St. Germain RM, Kuti JL, Doern GV, Girotto JE, **Nicolau DP**. Pharmacodynamic Target Attainment of Oral Beta-lactams for the Empiric Treatment of Acute Otitis Media in Children (Abstract No. 642, S07). 16th Pediatric Pharmacy Conference and Annual Meeting, Portsmouth, Virginia, September 2007

244a. Eagye KJ, Kim A, Laohavaleeson S, Kuti JK, **Nicolau DP**. Impact of Inadequate Antibiotic Therapy (IAT) on Hospital Length of Stay (LOS) in Patients with Complicated Skin and Skin Structure Infections (cSSSI). (Abstract No. K-1256). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

245a. Eagye KJ, **Nicolau DP**. Incidence of Infection and Impact on Hospital Length of Stay (LOS) and Costs in Patients Undergoing Elective Colorectal Surgery (ECS). (Abstract No. K-1127). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

246a. Kim A, Banevicius MA, **Nicolau DP**. *In Vivo* Efficacy of Doripenem Human Simulated Exposures against *Pseudomonas aeruginosa*. (Abstract No. A-32). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

ABSTRACTS (con't)

247a. Banevicius MA, Kaplan N., **Nicolau DP**. Comparative Dose Studies of API-1252 and Linezolid Against Community-Acquired Methicillin-Resistant *Staphylococcus aureus* in a Murine Pneumonia Model. (Abstract No. F1-930). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

248a. Laohavaleeson S, Lolans K, Quinn JP, Kuti JK, **Nicolau DP**. Identification of the MexXY-OprM Efflux System in Cefepime Resistant-Ceftazidime Susceptible *Pseudomonas aeruginosa* among Clinical Isolates from a US Hospital. (Abstract No. C2-1501). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

249a. Laohavaleeson S, Barriere SL, **Nicolau DP**, Kuti JK. Cost-effectiveness of Telavancin (TLV) versus Vancomycin (VAN) for the Treatment of Complicated Skin and Skin Structure Infections (cSSSI). (Abstract No. O-1871). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

250a. Laohavaleeson S, Tessier PR, **Nicolau DP**. Pharmacodynamic Characterization of Ceftobiprole in Pneumonia Caused by Phenotypically Diverse *Staphylococcus aureus*. (Abstract No. A-38). 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 17-20, 2007

251a. Laohavaleeson S, Barriere SL, **Nicolau DP**, Kuti JL. Cost-effectiveness of Telavancin versus Vancomycin for the Treatment of Complicated Skin and Skin Structure Infections. (Abstract No. 185E). American College of Clinical Pharmacy, 2007 Annual Meeting, Denver, CO, October 14-17, 2007

252a. Kim A, **Nicolau DP**, Kuti JL. Hospital Costs and Outcomes of Patients Discharged with a Diagnosis of Pulmonary Aspergillosis in the United States. (Abstract No. 189). American College of Clinical Pharmacy, 2007 Annual Meeting, Denver, CO, October 14-17, 2007

253a. Kim A, Banevicius MA, **Nicolau DP**. In Vivo Efficacy of Doripenem Human Simulated Exposures against *Pseudomonas aeruginosa*. (Abstract No. 109E). American College of Clinical Pharmacy, 2007 Annual Meeting, Denver, CO, October 14-17, 2007

254a. Kuti JL, Nicasio A, Shore E, Palter M, Pepe J, **Nicolau DP**. Outcomes of an Empiric Antibiotic Algorithm (EAA) for Ventilator Associated Pneumonia (VAP) that Considers Local MIC Distributions and Pharmacodynamics (Abstract No. 1026). 45th Annual Meeting of Infectious Diseases Society of America, San Diego, CA, October 4-7, 2007

ABSTRACTS (con't)

255a. Kim A, Sakoulas G, Kuti JL, **Nicolau DP**. Pharmacodynamic Analysis of Vancomycin versus Linezolid against Methicillin-Resistant Staphylococcus aureus Strains in New York (Abstract No. RP18) American Society of Hospital Pharmacists, 42nd Annual Midyear Clinical Meeting, Las Vegas, Nevada, December 2-6, 2007

256a. Crandon J, Kuti JL, Jones R, **Nicolau DP**. Pharmacodynamic Target Attainment Rates for 9 Antibiotics against Escherichia coli, Klebsiella spp., and Pseudomonas aeruginosa isolates in USA Hospitals. (Abstract No. 44). American College of Clinical Pharmacy, 2008 Spring Research and Practice Forum, Phoenix, AZ, April 5 - 9, 2008

David P. Nicolau, PharmD, FCCP

PRESENTATIONS

1989 - 1999 Presented 200 lecturers on various topics including clinical pharmacokinetics, pharmacodynamics, anti-infectives and general issues in infectious diseases and pharmacy practice to local, national and international audiences.

2000 - 2003 Presented 175 lecturers on various topics including clinical pharmacokinetics, pharmacodynamics, anti-infectives and general issues in infectious diseases and pharmacy practice to local, national and international audiences.

"New Therapies for Complicated Skin and Skin Structure Infections" CME lecture, Albany, New York, January 2004

"Emerging Resistance in Community-Acquired RTI Pathogen: Focus on the Pneumococcus" Making Informed Decisions Antimicrobial Advisory Board, Bonita Springs, Florida, January 2004

"Antimicrobial Pharmacodynamics: Implications for Clinical Practice" Academy for Infection Management (AIM) Educational Summit Meeting, Berlin, Germany, February 2004

"Optimising Antimicrobial Activity: the OPTAMA Programme" Academy for Infection Management (AIM) Educational Summit Meeting, Berlin, Germany, February 2004

"Antibiotic Activity, Drug Delivery Time, and the Risk of Resistance" CARTIs in the Crossfire: A Cased-Based Approach on the Emerging Opinions on Antibiotic Management, CME Symposium conducted during the 41st Annual American College of Osteopathic Family Physicians (ACOFP), Tampa, Florida, March 2004

"Choosing an Antibiotic Regimen for Optimal Therapeutic Effect: Specific PK/PD Considerations" Clinical Medicine Today, Video Conference Series, March – November 2004

"Contemporary Strategies for Reducing Antibiotic Resistance" Contemporary Strategies for Reducing Antibiotic Resistance, Symposia conducted during the 2004 Academy of Managed Care Pharmacists Annual Meeting & Showcase, San Francisco, California, March 2004

"Antibiotic Activity, Drug Delivery Time and the Risk of Resistance" CARTIs in the Crossfire: A Cased-based Approach on the Emerging Opinions of Antibiotic Management, PriMed South Meeting, Ft. Lauderdale, Florida, April 2004

"Optimizing Antimicrobial Therapy" Infection 2004: Maximizing the Probability of Positive Outcomes, 3rd Annual Meeting, Program Chair & Speaker, Dallas (Frisco), Texas, April 2004

PRESENTATIONS (con't)

"Optimizing Clinical and Microbiologic Outcomes in the ICU" Clinical Approaches to Overcoming Bacterial Resistance in Serious Nosocomial Pathogens, VHA TV Live Satellite Broadcast, Part One, Dallas, Texas, May 2004

"Meeting the Challenges of ICU Related Infection" Clinical Approaches to Overcoming Bacterial Resistance in Serious Nosocomial Pathogens, VHA TV Live Satellite Broadcast, Part Two, Dallas, Texas, May 2004

"Criteria for Selection: Optimizing Antimicrobial Effectiveness" CARTIs in the Crossfire: A Case-Based Approach on the Emerging Opinion of Antibiotic Management, Symposium conducted during the 100th International Conference of the American Thoracic Society, Orlando, Florida, May 2004

"Approaches to Responsible Use of Antibacterial Agents" Meeting the Challenges of Bacterial Resistance in Serious Nosocomial Infections – Strategies for Improving Patient Outcomes, Series Editorial Board Chairman and Speaker, Maimonides Medical Center, Brooklyn, NY, June 2004

"Strategic Selection of Antibiotics in the Management of Community-Acquired Respiratory Tract Infections" National Coalition of Medical, Pharmacy, Managed Care and Health Related Business Associations, Washington, D.C., June 2004

"Strategic Selection of Antibiotics for Respiratory Tract Infections" State of the Art Lecture, 32nd Annual Meeting of the American Academy of Physician Assistants, Las Vegas, Nevada, June 2004

"Factors in Antibiotic Selection" Mind Your Microbes: Macrolides for RTI; The Past, Present, and Opportunities to Improve the Future, Symposium conducted during the 32nd Annual Meeting of the American Academy of Physician Assistants, Las Vegas, Nevada, June 2004

"Antimicrobial Factors that Minimize the Risk of Resistance" Think Twice, Prescribe Once: Empiric Management of Respiratory Tract Infections, Symposium conducted during the 19th Annual Meeting of the American Academy of Nurse Practitioners, New Orleans, Louisiana, June 2004

"Adequate Empirical Therapy – Revisions of Evidences" Academy for Infection Management (AIM) Educational Meeting, Co-Chairman and Speaker, Club Med Itaparrica Hotel, Vera-Cruz – Bahia, Brazil, June 2004

PRESENTATIONS (con't)

"Pharmacodynamics and Clinical Implications" Academy for Infection Management (AIM) Educational Meeting, Co-Chairman and Speaker, Club Med Itaparrica Hotel, Vera-Cruz – Bahia, Brazil, June 2004

"Overview of Nosocomial Pneumonia and Complicated Skin and Soft Tissue Infections Caused by MRSA: Treatment Strategies and Outcome Analysis" Nosocomial Pneumonia and Complicated Skin and Soft Tissue Infections Caused by MRSA: Overview and Health Economics, Symposium conducted during the Annual Meeting of the Florida Society of Health-Systems Pharmacist, Orlando, Florida, August 2004

"Consideration in Antibiotic Selection" Petri vs. people: You be the Judge, Pri-Med Update Symposium Series, Washington, D.C., September 2004

"Overview of Nosocomial Pneumonia and Complicated Skin and Soft Tissue Infections Caused by MRSA: Treatment Strategies and Outcome Analysis" Nosocomial Pneumonia and Complicated Skin and Soft Tissue Infections Caused by MRSA: Overview and Health Economics, Symposium conducted during the Annual Meeting of the Illinois Society of Health-Systems Pharmacist, Oakbrook Terrace, Illinois, September 2004

"Antibiotics in ENT: Focus on Community-Acquired Respiratory Tract Infections" Society of Otorhinolaryngology and Head-Neck Nurses, 28th Annual Congress and Nursing Symposium, New York, New York, September 2004

"Decreasing the Development of Resistance", Achieving the Best Fit: Value and Consequences of Tailoring the Antibiotic in respiratory Tract infections, Symposium conducted during the Infectious Diseases Society of America, Boston, MA, September 2004

"Optimizing Antimicrobial Activity with PK/PD Application", Mid-Atlantic Regional Infection Management Education Summit, Baltimore, Maryland, October 2004

"Antibiotic factors that Minimize the Potential for Future Resistance", Management of Community-Acquired Respiratory Tract Infections inn the Era of Growing Resistance: Implications for Formulary Decision-Making, Symposium conducted during the Academy of Managed Care Pharmacy, Baltimore, Maryland, October 2004

"Chemical Properties Affect the Likelihood of Developing Resistance", Achieving the Best Fit: Value and Consequences of Tailoring the Antibiotic in respiratory Tract infections, Symposium conducted during the Scientific Assembly of the American College of Emergency Physicians, San Francisco, CA, October 2004

PRESENTATIONS (con't)

"Resistant Pathogens: Case-based Lessons in the Treatment of Skin and Soft Tissue Infection: Community-Acquired vs. Hospital Acquired MRSA", Therapeutic Decision-Making in Infectious Diseases: Current Strategies and Future Possibilities, Symposium conducted during the Annual Meeting of the American College of Clinical Pharmacy, Dallas, TX, October 2004

"Chemical Properties Affect the Likelihood of Developing Resistance", Optimizing Antimicrobial Therapy in the Empiric Management of Respiratory Tract Infections, Symposium conducted during the Annual Meeting of the American College of Clinical Pharmacy, Dallas, TX, October 2004

"Challenges in the Management of Complicated Skin and Skin Structure Infections", Introduction of New Therapeutic Options for Treatment of Polymicrobial Pathogens, Symposium conducted during the American Society of Health-System Pharmacists, 39th Annual Midyear Clinical Meeting, Orlando, Florida, December 2004

"Chemical Properties Affect the Likelihood of Developing Resistance", Optimizing Antimicrobial Therapy in the Empiric Management of Respiratory Tract Infections, Symposium conducted during the American Society of Health-System Pharmacists, 39th Annual Midyear Clinical Meeting, Orlando, Florida, December 2004

"Decreasing the Development of Resistance in CARTIs", Treating Respiratory Tract Infections: Manage the Patient, Manage the Community, Symposium conducted during the PriMed Southwest Meeting, Houston, Texas, January 2005

"New Antibiotic Therapies in the Treatment of Respiratory Tract Infections", Treating Respiratory Tract Infections: Manage the Patient, Manage the Community, Symposium conducted during the PriMed Southwest Meeting, Houston, Texas, January 2005

"How Can We Control Antimicrobial Resistance?", 12th Annual First Coast Infectious Disease/Clinical Microbiology Symposium, St. Augustine, Florida, February 2005

"Tailor the Treatment", Treating Respiratory Tract Infections: Manage the Patient - Manage the Community, Symposium conducted during the Annual Meeting of the American College of Osteopathic Family Physicians, Phoenix, Arizona, March 2005

"Are We getting It Right First Time? The AIM Audit Tools" Academy for Infection management: Getting Therapy Right First Time Through Education, Symposium conducted prior to 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2005

PRESENTATIONS (con't)

"Pharmacodynamic Evaluation of Current Agents for Serious Hospital Infection: Are We getting it Right? Facing the Future: Challenges and Solutions in the treatment of Serious Hospital Infections, Symposium conducted during the 15th European Congress of Clinical Microbiology and Infectious Diseases, Copenhagen, Denmark, April 2005

"Pharmacodynamic Considerations When Optimizing VAP Therapy" 2nd Annual New England Critical Care Pharmacy Symposium, Northeastern University, Bouve College of Health Sciences, Boston, Massachusetts, April 2005

"Optimizing Antimicrobial Efficacy: Minimizing Resistance" Infection 2005: Maximizing the Probability of Positive Outcomes, 4th Annual Meeting, Program Chair & Speaker, Orlando, Florida, April 2005

"Optimizing Antimicrobial Efficacy in the Face of Rising Resistance?" The Pus Club, Charlotte, North Carolina, May 2005

"Antimicrobial Resistance Among Gram-Positive Pathogens: Review of Epidemiological Characteristics and Treatment Options for MRSA" Continuing Education Teleconference Series, University of Buffalo College of Pharmacy, 6 lecture series, May – June 2005

"Acute bacterial Exacerbation of Chronic Bronchitis: Current State of the Disease and Value of Appropriate Antibiotic Therapy" PriMed City Update, Hartford, Connecticut, June 2005

"Therapeutic Options for the Treatment of Respiratory Tract Infections" Antimicrobial Resistance: An Evolving Challenge in the Treatment of Respiratory Tract Infections, Live Satellite Broadcast, 2005 Clinical Medicine Today, Milwaukee, Wisconsin, June 2005

"Optimizing Infection Related Outcomes due to Streptococci, Staphylococci and Enterococci in the Era of Increasing Resistance" Alabama Society of Health-System Pharmacist, Summer Meeting & Exhibition, Destin, Florida, July 2005

"Decreasing the Development of Resistance" Treating Respiratory Tract Infections: Manage the Patient, Manage the Community, PriMed Mid-Atlantic Meeting, Baltimore, Maryland, October 2005

"Pharmacodynamic Applications to Optimize Efficacy" Beijing, Shanghai and Guangzhou, China, December 2005

"Optimizing Infection Management in the Hospitalized Patients" Beijing, China, December 2005

PRESENTATIONS (con't)

"Maximizing Antimicrobial Outcomes: Understanding the Obstacles" Infection 2006: Maximizing the Probability of Positive Outcomes, 5th Annual Meeting, Program Chair & Speaker, Las Vegas, Nevada, February 2006

"New Opportunities for Old Antibiotics Derived from New PK/PD Data" Gentamicin 40 Years of Clinical Practice, Mexico City, Mexico, February 2006

"Pharmacokinetic and Pharmacodynamics of Tigecycline" Facing the Future: Challenges and Solutions in the Treatment of Serious Hospital Infections, Cartagena, Colombia, March 2006

"The Role of the Pharmacologist: Are There Any Successful Pharmacological Strategies to Decrease Resistance in Gram+ Bacteria" IV International Symposium on Antimicrobial Resistance, Cartagena, Colombia, March 2006

"Is More Better: Monotherapy versus Combination Therapy" IV International Symposium on Antimicrobial Resistance, Cartagena, Colombia, March 2006

"Optimizing Therapy with PK/PD Applications" IV International Symposium on Antimicrobial Resistance, Cartagena, Colombia, March 2006

"Resistant Infections: Considering the Options for Antibiotic Treatment of Serious Bacterial Infections" Teleconference series, Princeton Media Associates, Englishtown, NJ, 6 lecture series, March 2006

"Pharmacodynamic Applications to Optimizing Antimicrobial Efficacy" 1st Congress of Yugoslav Society for Antimicrobial Chemotherapy, venue Sava Centre, Belgrade, Serbia & Montenegro, March 2006

"Optimizing Infection Outcomes in the Era of Multi-drug Resistant Pathogens" Teleconference Series, Schentag Corporation, Buffalo, NY, 8 lecture series, March - May 2006

"Optimizing Antibiotic Treatment in Serious Infections: Pharmacodynamic Implications" Six city Lecture series (Delhi, Lucknow, Calcutta, Chennai, Ahmedabad, Bombay) in India, April 2006

"A Strategic Approach to Control of Hospital Acquired Infections" Co-presented with Dr. Phillip Barie, VHA Leadership Conference, St. Louis, Missouri, May 2006

"New Opportunities for Old Antibiotics Derived from New Pharmacokinetic-Pharmacodynamic Data" Symposium conducted during the 31st National Infectology Congress, Monterrey, Mexico, July 2006

PRESENTATIONS (con't)

"Optimizing Antimicrobial Efficacy in the Era of Resistance: Focus on Hospitalized Patient" Medical Grand Rounds, Royal University, Saskatoon City and St. Paul's Hospitals, Saskatoon, Canada, August 2006

"Optimizing Antimicrobial Efficacy in the Era of Resistance: Focus on Hospitalized Patient" The Pus Club, Carolina Medical Center, Charlotte, North Carolina, September 2006

"Pharmacokinetics of Levofloxacin 750 mg Once-daily in Patients with Acute Exacerbation of Chronic Bronchitis" (Abstract No. A0332). 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, September 2006

"Contemporary Issues in the Management of Gram-Positive Resistance: Focus on the Staphylococcus" Hospital Pharmacists of Western Massachusetts, Springfield, MA, October 2006

"Optimal Use of Carbapenems: Pharmacokinetics/Pharmacodynamics and De-escalation Therapy" Medical Tribune Roundtable, Hotel Okura, Fukuoka, Japan, December 2006

"Optimizing Antimicrobial Therapy in the Era of Resistance" Medical Grand Rounds, Peking University Medical College Hospital, Beijing, China, December 2006

"Optimizing Antimicrobial Therapy in the Face of Global Resistance" Continuing Education Program, Seminar on Optimizing Antimicrobial Therapy, Beijing News Plaza, Beijing, China, December 2006

"Optimizing Antimicrobial Therapy in the Era of Resistant: Application from the Bench to the Bedside" All School Seminar, School of Pharmacy, University of Connecticut, Storrs, CT, February 2007

"Optimizing Antibacterials in the Era of Resistance" Infectious Disease Conference, Mt. Sinai Hospital, New York, NY, February 2007

"Considerations for the Use of Tigecycline" Symposium conducted during the VIII Colombia Congress of Infectious Diseases, Bogota, Colombia, June 2007

"Pharmacodynamics: Application to the Care of Critically Ill Patient" VIII Colombia Congress of Infectious Diseases, Bogota, Colombia, June 2007

"IDSA / ATS Community-acquired Pneumonia (CAP) Guidelines: Advances and Caveats" VIII Colombia Congress of Infectious Diseases, Bogota, Colombia, June 2007

PRESENTATIONS (con't)

"Target Attainment: Is this Important?" Academy for Infection Management, 3rd Latin American Summit Meeting, Guadalajara, Mexico, June 2007

"Current Resistance Trends in Latin America" Academy for Infection Management, 3rd Latin American Summit Meeting, Guadalajara, Mexico, June 2007

"*Staphylococcus aureus* Infections: New Challenges from an Old Pathogen" China Summit for Gram-positive Infections, Shanghai, China, August 2007

"New Challenges from *Staphylococcus aureus*" Asia Cubicin Expert Forum, Shanghai, China, September 2007

"Optimizing Infection Outcomes: Consideration of the 3Ds (Drug, Dose, Duration)" Antibiotic Resistance Among Bacterial Pathogens: Mechanisms, Detection and Molecular Epidemiology (Workshop: 47-06). Workshop conducted during the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 2007

"Where Should You Use Pulse Dosing?" Building a Better Mousetrap for MDR Pathogens: Using Available Resources to Optimize the Antibiotic Regimen (Session198A / 146). Symposium conducted during the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, IL, September 2007

"Optimizing Antibacterial Therapy: Focus on the Critically Ill Patient" Surgical Grand Rounds – Academic Half-Day Program, Vancouver General Hospital, Vancouver, Canada, September 2007

"Treatment of MRSA with Vancomycin: Resistance and Dosing Issues" Infectious Diseases Conference, Stony Brook University Hospital, Stony Brook, New York, January 2008

"Optimizing Antimicrobial Efficacy: Application of Pharmacodynamic Principles" Infection Diseases Conference, New York Hospital Queens, Flushing, New York, January 2008

"Treatment of MRSA: Optimizing Outcomes in the Era of Increasing Prevalence" Internal Medicine Noon Conference, Nassau University Medical Center, East Meadow, New York, January 2008

"Optimizing Antimicrobial Efficacy: In the Face of Resistance" Infection Infectious Diseases Lecture Series, Long Island Jewish Hospital, New Hyde Park, New York, January 2008

PRESENTATIONS (con't)

"Optimizing dosing strategies for today's antimicrobials" An Erupting Landscape: Nosocomial Pneumonia in the Age of Resistance. Symposium conducted during the Society of Critical Care Medicine's 37th Critical Care Congress, Honolulu, HI, February 2008

"Adverse Events w/ new Antimicrobials" 34th Remington Winter Course in Infectious Diseases, 200 Winter Course, Sun Valley, ID, March 2008

"Antibiotic Pharmacodynamics: Clinical Utilization" 34th Remington Winter Course in Infectious Diseases, 200 Winter Course, Sun Valley, ID, March 2008

"Maximizing Antimicrobial Pharmacodynamics in the Treatment of Resistant Gram-Negative Infections" Symposium conducted during the 2008 Annual Conference of the National Home Infusion Association, Phoenix, AZ, March 2008

David P. Nicolau, PharmD, FCCP

TEACHING

Medical University of South Carolina, College of Pharmacy, Charleston, South Carolina

Clinical Assistant Professor July 1990 - June 1991

Butler University, College of Pharmacy, Indianapolis, Indiana

Adjunct Assistant Professor July 1994 - June 1998

Idaho State University, College of Pharmacy, Pocatello, ID

Adjunct Assistant Professor July 1994 - present

University of Connecticut, School of Pharmacy, Storrs, Connecticut

Assistant Clinical Professor July 1991 - September 1994

Associate Clinical Professor September 1994 – present

Union University, Albany College of Pharmacy, Albany, New York

Adjunct Assistant Professor July 1999 – July 2000

SCIENTIFIC REVIEWER/EDITORIAL BOARD/EDITOR

Annals of Pharmacotherapy
Antimicrobial Agents & Chemotherapy
Editorial Board 2000 – 2001
Antibiotics for the Clinician
Editorial Board 1996 -
Chemotherapy
Editorial Board 2002 -
Clinical Infectious Diseases
Clinical Pharmacokinetics
Critical Care Medicine
Diagnostic Microbiology and Infectious Disease
Editorial Board 1998 -
European Journal of Clinical Microbiology and Infectious Diseases
Expert Opinion on Pharmacotherapy
Editorial Board 2006 -
Infectious Diseases in Clinical Practice (IDCP)
Editorial Board 2005 -
Journal of American Medical Association
Journal of Antimicrobial Chemotherapy
Journal of Infectious Disease Pharmacotherapy
Editorial Board 1996 - 1999
Co-Editor 2000 - 2004
Laboratory Animal Science
PharmacoEconomics
Pharmacotherapy
PharmacoEconomics: Infectious Diseases
Editorial Board 1997 - 2000 (Publication halted)
Pharmacy Practice News
Editorial Board 2004 -
Surgical Infections
Editorial Board 2002 -

AHFS Drug Information (1995 ed.)

Basic Skills in Interpreting Laboratory Data, ASHP, (Second ed., 1995)

ASHP Therapeutic Guidelines, Antimicrobial Prophylaxis in Surgical and Nonsurgical Procedures 1999

APHA Special Report, Combating Antibiotic Resistance, Advisory Board, 2001

David P. Nicolau, PharmD, FCCP

PROFESSIONAL ORGANIZATIONS

1987 - 1988, 1991 - **New England Council of Hospital Pharmacists**

Program Co-chairperson, 24th Annual Fall Seminar, October 27, 1992
"An Update on the Treatment of HIV Disease"

Program Co-chairperson, 27th Annual Fall Seminar, October 17, 1995
"Current Issues in Pharmacy Practice"

1993 - 1994 President-Elect

1994 - 1995 President

1988 - **American Society of Hospital Pharmacists**

1990 - **ASHP Infectious Diseases Special Practice Group**

1990 - **American Society for Microbiology**

1990 - **American College of Clinical Pharmacy**

1995 - 1996 Research Affairs Committee

1997 - Pharmacokinetics/Pharmacodynamics PRN

1998 - Infectious Diseases PRN

1998 - Outcomes and Economics PRN

1999 Granted, Amgen Biotechnology Award

2000 - 2002 Fellowship Review Committee

2000 Abstract Reviewer, Spring Practice and Research Forum

2000 Elected, Fellow College of Clinical Pharmacy

1992 - **New England College of Clinical Pharmacy**

1992 - **Society of Infectious Diseases Pharmacists**

1996 - 1997 Finance Committee

1997 - 1998 Ortho-McNeil Visiting Practitioner Award

1998 Granted, SIDP Research Award

1999 - 2000 Program Committee

1994 - **Connecticut Infectious Diseases Society**

1994 - **Infectious Diseases Society of America**

1996 - **International Society for Anti-Infective Pharmacology**

EPA/600/Z-92/001
May 1992

Guidelines for Exposure Assessment

Published on May 29, 1992, Federal Register 57(104):22888-22938

These guidelines replace the previously issued final Guidelines for Estimating Exposures (September 24, 1986), Federal Register 51(185):34042-34054, and the Proposed Guidelines for Exposure-Related Measurements (December 2, 1988), Federal Register 53(232):48830-48853.

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Note: This document represents the final guidelines. A number of editorial corrections have been made during conversion and subsequent proofreading to ensure the accuracy of this publication.

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GUIDELINES FOR EXPOSURE ASSESSMENT
[FRL-4129-5]

AGENCY: U.S. Environmental Protection Agency

ACTION: Final Guidelines for Exposure Assessment

SUMMARY: The U.S. Environmental Protection Agency (EPA) is today issuing final guidelines for exposure assessment. The Guidelines for Exposure Assessment (hereafter "Guidelines") are intended for risk assessors in EPA, and those exposure and risk assessment consultants, contractors, or other persons who perform work under Agency contract or sponsorship. In addition, publication of these Guidelines makes information on the principles, concepts, and methods used by the Agency available to all interested members of the public. These Guidelines supersede and replace both the Guidelines for Estimating Exposures published September 24, 1986 (51 FR 34042-34054) (hereafter "1986 Guidelines") and the Proposed Guidelines for Exposure-Related Measurements published for comment on December 2, 1988 (53 FR 48830-48853) (hereafter "1988 Proposed Guidelines"). In response to recommendations from the Science Advisory Board (SAB) and the public, the 1986 Guidelines were updated and combined with the 1988 Proposed Guidelines and retitled as the current Guidelines for Exposure Assessment.

These Guidelines establish a broad framework for Agency exposure assessments by describing the general concepts of exposure assessment including definitions and associated units, and by providing guidance on the planning and conducting of an exposure assessment. Guidance is also provided on presenting the results of the exposure assessment and characterizing uncertainty. Although these Guidelines focus on exposures of humans to chemical substances, much of the guidance contained herein also pertains to assessing wildlife exposure to chemicals, or human exposures to biological, noise, or radiological agents. Since these latter four areas present unique challenges, assessments on these topics must consider additional factors beyond the scope of these Guidelines. The Agency may, at a future date, issue additional specific guidelines in these areas.

EFFECTIVE DATE: The Guidelines will be effective May 29, 1992.

FOR FURTHER INFORMATION, CONTACT: Michael A. Callahan, Director, National Center for Environmental Assessment-Washington Division (8623D), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460, TEL: 202-564-3259.

SUPPLEMENTARY INFORMATION: In its 1983 book *Risk Assessment in the Federal Government: Managing the Process*, the National Academy of Sciences recommended that Federal regulatory agencies establish "inference guidelines" to promote consistency and technical quality in risk assessment, and to ensure that the risk assessment process is maintained as a scientific effort separate from risk management. A task force within EPA accepted that recommendation and requested that Agency scientists begin to develop such guidelines.

In 1984, EPA scientists began work on risk assessment guidelines for carcinogenicity, mutagenicity, suspect developmental toxicants, chemical mixtures, and estimating exposures. Following extensive scientific and public review, these guidelines were issued on September 24, 1986 (51 FR 33992-34054). Subsequent work resulted in the publishing of four additional proposals (one of which has recently become final): Proposed Guidelines for Assessing Female Reproductive Risk (53 FR 24834-24847), Proposed Guidelines for Assessing Male Reproductive Risk (53 FR 24850-24869), Proposed Guidelines for Exposure-Related Measurements (53 FR 48830-48853), and Proposed Amendments to the Guidelines for the Health Assessment of Suspect Developmental Toxicants (54 FR 9386-9403). The final Guidelines for Developmental Toxicity Risk Assessment, published December 5, 1991 [56 FR 63798-63826], supersede and replace the proposed amendments.

The Guidelines issued today continue the guidelines development process initiated in 1984. Like the guidelines issued in 1986, the Guidelines issued today set forth principles and procedures to guide EPA scientists in the conduct of Agency risk assessments and to inform Agency decision makers and the public about these procedures. In particular, the Guidelines standardize terminology used by the Agency in exposure assessment and in many areas outline the limits of sound scientific practice. They emphasize that exposure assessments done as part of a risk assessment need to consider the hazard identification and dose-response parts of the risk assessment in the planning stages of the exposure assessment so that these three parts can be smoothly integrated into the risk characterization. The Guidelines discuss and reference a number of approaches and tools for exposure assessment, along with discussion of their appropriate use. The Guidelines also stress that exposure estimates along with supporting information will be fully presented in Agency risk assessment documents, and that Agency scientists will identify the strengths and weaknesses of each assessment by describing uncertainties, assumptions, and limitations, as well as the scientific basis and rationale for each assessment.

Work on these Guidelines began soon after publication of the 1986 Guidelines. At that time, the SAB recommended that the Agency develop supplementary guidelines for conducting exposure studies. This supplementary guidance was developed by an Agency work group composed of scientists from throughout the Agency, a draft was peer reviewed by experienced

professionals from environmental groups, industry, academia, and other governmental agencies, and proposed for comment on December 2, 1988 (as Proposed Guidelines for Exposure-Related Measurements). In the public notice, the Agency asked for comment on whether the proposed guidelines should be combined with the 1986 guidelines in order to have a single Agency guideline for exposure assessment. Comments from the public and the SAB were heavily in favor of combining the two guidelines.

Since proposal, the Agency has reformatted the 1988 Proposed Guidelines to allow incorporation of the information in the 1986 Guidelines, and incorporated revisions resulting from additional public and SAB comments, to establish the current Guidelines. The current Guidelines were reviewed by the Risk Assessment Forum and the Risk Assessment Council, subjected to an external peer review, and presented to the SAB on September 12, 1991 for final comment (EPA-SAB-IAQC-92-015). In addition, the Guidelines were reviewed by the Working Party on Exposure Assessment, an interagency working group under the Subcommittee on Risk Assessment of the Federal Coordinating Committee on Science, Engineering and Technology. Comments of these groups have been considered in the revision of these Guidelines. The full text of the final Guidelines for Exposure Assessment is published here.

These Guidelines were developed as part of an interoffice guidelines development program under the auspices of the Risk Assessment Forum and the Office of Health and Environmental Assessment in the Agency's Office of Research and Development. The Agency is continuing to study risk assessment issues raised in these Guidelines, and will revise them in line with new information as appropriate.

Following this preamble are two parts: Part A is the Guidelines and Part B is the Response to the Public and Science Advisory Board comments submitted in response to the 1988 Proposed Guidelines.

References, supporting documents, and comments received on the 1988 Proposed Guidelines, as well as a copy of these final Guidelines for Exposure Assessment are available for inspection and copying at the Public Information Reference Unit Docket (202-260-5926), EPA Headquarters Library, 401 M Street, S.W., Washington, DC, between the hours of 8:00 a.m. and 4:30 p.m.

Dated: April 28, 1992

Signed by EPA Administrator
William K. Reilly

ABBREVIATIONS AND ACRONYMS

ADD	Average daily dose
AF	Absorption fraction
AT	Averaging time
BW	Body weight
C	Exposure concentration
C(t)	Exposure concentration as a function of time
CO	Carbon monoxide
CT	Contact time
D	Dose
D_{app}	Applied dose
D_{int}	Internal dose
D_{pot}	Potential dose
DQO	Data quality objective
E	Exposure
ED	Exposure duration
EPA	U.S. Environmental Protection Agency
F_{adh}	Adherence factor for soil
f(t)	Absorption function
IR	Intake rate (also ingestion or inhalation rate)
J	Flux
K_p	Permeability coefficient
LADD	Lifetime average daily dose
LOAEL	Lowest observable adverse effect level
LOD	Limit of detection
LT	Lifetime
M_{medium}	Amount (mass) of carrier medium material applied to the skin
MDL	Method detection limit
MEI	Maximum exposed individual or maximally exposed individual
ND	Not detected
PMN	Premanufacture notice
QA	Quality assurance
QAP_jP	Quality assurance project plan
QC	Quality control
QL	Quantification limit

ABBREVIATIONS AND ACRONYMS (continued)

RfC	Reference concentration
RfD	Reference dose
SA	Surface area
SAB	Science Advisory Board
TEAM	Total exposure assessment methodology
TUBE	Theoretical upper bounding estimate
UCL	Upper confidence limit (often used to refer to the upper confidence limit of the mean)
UR	Uptake rate

PART A: GUIDELINES FOR EXPOSURE ASSESSMENT

1. INTRODUCTION

In 1984, the U.S. Environmental Protection Agency (EPA) initiated a program to ensure scientific quality and technical consistency of Agency risk assessments. One of the goals of the program was to develop risk assessment guidelines that would be used Agencywide. The guidelines development process includes a public review and comment period for all proposed guidelines as well as Agency Science Advisory Board review. Following the review process, the guidelines are revised if needed and then issued as final guidelines. The Guidelines for Estimating Exposures (hereafter "1986 Guidelines") were one of five guidelines issued as final in 1986 (U.S. EPA, 1986a). In 1988, the Proposed Guidelines for Exposure-Related Measurements (hereafter "1988 Proposed Guidelines") were published in the Federal Register for public review and comment (U.S. EPA, 1988a). The 1988 Proposed Guidelines were intended to be a companion and supplement to the 1986 Guidelines.

When proposing the 1988 guidelines, the Agency asked both the EPA Science Advisory Board (SAB) and the public for comments on combining the 1986 and 1988 exposure guidelines into a larger, more comprehensive guideline; the majority of comments received were in favor of doing so. Thus, these 1992 Guidelines For Exposure Assessment (hereafter "Guidelines") combine, reformat, and substantially update the earlier guidelines. These guidelines make use of developments in the exposure assessment field since 1988, both revising the previous work and adding several topics not covered in the 1986 or 1988 guidelines. Therefore, the 1992 guidelines are being issued by the Agency as a replacement for both the 1986 Guidelines and the 1988 Proposed Guidelines.

1.1. INTENDED AUDIENCE

This document is intended for exposure and risk assessors in the Agency and those exposure and risk assessment consultants, contractors, or other persons who perform work under Agency contract or sponsorship. Risk managers in the Agency may also benefit from this document since it clarifies the terminology and methods used by assessors, which in some cases could strengthen the basis for decisions. In addition, publication of these guidelines makes information on the principles, concepts, and methods used by the Agency available to other agencies, States, industry, academia, and all interested members of the public.

1.2. PURPOSE AND SCOPE OF THE GUIDELINES

There are a number of different purposes for exposure assessments, including their use in risk assessments, status and trends analysis, and epidemiology. These Guidelines are intended to convey the general principles of exposure assessment, not to serve as a detailed instructional guide. The technical documents cited here provide more specific information for individual exposure assessment situations. As the Agency performs more exposure assessments and incorporates new approaches, these Guidelines will be revised.

Agency risk assessors should use these Guidelines in conjunction with published guidelines for assessing health effects such as cancer (U.S. EPA, 1986b), developmental toxicity (U.S. EPA, 1991a), mutagenic effects (U.S. EPA, 1986c), and reproductive effects (U.S. EPA, 1988b; U.S. EPA, 1988c). These exposure assessment guidelines focus on human exposure to chemical substances. Much of the guidance contained herein also applies to wildlife exposure to chemicals, or human exposure to biological, physical (i.e., noise), or radiological agents. Since these areas present unique challenges, however, assessments on these topics must consider additional factors beyond the scope of these Guidelines.

For example, ecological exposure and risk assessment may deal with many species which are interconnected via complex food webs, while these guidelines deal with one species, humans. While these guidelines discuss human exposure on the individual and population levels, ecological exposure and risk assessments may need to address community, ecosystem, and landscape levels, also. Whereas chemical agents may degrade or be transformed in the environment, biological agents may of course grow and multiply, an area not covered in these guidelines. The Agency may, at a future date, issue specific guidelines in these areas.

Persons subject to these Guidelines should use the terms associated with chemical exposure assessment in a manner consistent with the glossary in Section 8. Throughout the public comment and SAB review process, the Agency has sought definitions that have consensus within the scientific community, especially those definitions common to several scientific fields. The Agency is aware that certain well understood and widely accepted concepts and definitions in the area of health physics (such as the definition of exposure) differ from the definitions in this glossary. The definitions in this glossary are not meant to replace such basic definitions used in another field of science. It was not possible, however, to reconcile all the definitions used in various fields of science, and the ones used in the glossary are thought to be the most appropriate for the field of chemical exposure assessment.

The Agency may, from time to time, issue updates of or revisions to these Guidelines.

1.3. ORGANIZATION OF THE GUIDELINES

These Guidelines are arranged in an order that assessors commonly use in preparing exposure assessments. Section 2 deals with general concepts, Section 3 with planning, Section 4 with data development, Section 5 with calculating exposures, Section 6 with uncertainty evaluation, and Section 7 with presenting the results. In addition, these Guidelines include a glossary of terms (Section 8) and references to other documents (Section 9).

2. GENERAL CONCEPTS IN EXPOSURE ASSESSMENT

Exposure assessment in various forms dates back at least to the early twentieth century, and perhaps before, particularly in the fields of epidemiology (World Health Organization [WHO], 1983), industrial hygiene (Cook, 1969; Paustenbach, 1985), and health physics (Upton, 1988). Epidemiology is the study of disease occurrence and the causes of disease, while the latter fields deal primarily with occupational exposure. Exposure assessment combines elements of all three disciplines. This has become increasingly important since the early 1970s due to greater public, academic, industrial, and governmental awareness of chemical pollution problems.

Because there is no agreed-upon definition of the point on or in the body where exposure takes place, the terminology used in the current exposure assessment literature is inconsistent. Although there is reasonable agreement that human exposure means contact with the chemical or agent (Allaby, 1983; Environ Corporation, 1988; Hodgson et al., 1988; U.S. EPA, 1986a), there has not yet been widespread agreement as to whether this means contact with (a) the visible exterior of the person (skin and openings into the body such as mouth and nostrils), or (b) the so-called exchange boundaries where absorption takes place (skin, lung, gastrointestinal tract).[1] These different definitions have led to some ambiguity in the use of terms and units for quantifying exposure.[2]

Comments on the 1986 Guidelines and the 1988 Proposed Guidelines suggested that EPA examine how exposure and dose were defined in Agency assessments and include guidance on appropriate definitions and units. After internal discussions and external peer review, it is the Agency's position that defining exposure as taking place at the visible external boundary, as in (a) above, is less ambiguous and more consistent with nomenclature in other scientific fields. This is a change from the 1986 Guidelines.

Under this definition, it is helpful to think of the human body as having a hypothetical outer boundary separating inside the body from outside the body. This outer boundary of the body is the skin and the openings into the body such as the mouth, the nostrils, and punctures

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[1]A third, less common, scheme is that exposure is contact with any boundary outside or inside of the body, including internal boundaries around organs, etc. This scheme is alluded to, for example, in an article prepared by the National Research Council (NRC, 1985, p. 91). One could then speak of exposure to the whole person or exposure to certain internal organs.

[2]For example, the amount of food ingested would be a dose under scheme (a) and an exposure under scheme (b). Since the amount ingested in an animal toxicology study is usually termed administered dose, this leads to the use of both exposure and dose for the same quantity under scheme (b). There are several such ambiguities in any of the currently used schemes. Brown (1987) provides a discussion of various units used to describe exposures due to multiple schemes.

and lesions in the skin. As used in these Guidelines, exposure to a chemical is the contact of that chemical with the outer boundary. An exposure assessment is the quantitative or qualitative evaluation of that contact; it describes the intensity, frequency, and duration of contact, and often evaluates the rates at which the chemical crosses the boundary (chemical intake or uptake rates), the route by which it crosses the boundary (exposure route; e.g., dermal, oral, or respiratory), and the resulting amount of the chemical that actually crosses the boundary (a dose) and the amount absorbed (internal dose).

Depending on the purpose for which an exposure assessment will be used, the numerical output of an exposure assessment may be an estimate of either exposure or dose. If exposure assessments are being done as part of a risk assessment that uses a dose-response relationship, the output usually includes an estimate of dose.[3] Other risk assessments, for example many of those done as part of epidemiologic studies, use empirically derived exposure-response relationships, and may characterize risk without the intermediate step of estimating dose.

2.1. CONCEPTS OF EXPOSURE, INTAKE, UPTAKE, AND DOSE

The process of a chemical entering the body can be described in two steps: contact (exposure), followed by actual entry (crossing the boundary). Absorption, either upon crossing the boundary or subsequently, leads to the availability of an amount of the chemical to biologically significant sites within the body (internal dose[4]). Although the description of contact with the outer boundary is simple conceptually, the description of a chemical crossing this boundary is somewhat more complex.

There are two major processes by which a chemical can cross the boundary from outside to inside the body. Intake involves physically moving the chemical in question through an opening in the outer boundary (usually the mouth or nose), typically via inhalation, eating, or drinking. Normally the chemical is contained in a medium such as air, food, or water; the estimate of how much of the chemical enters into the body focuses on how much of the carrier medium enters. In this process, mass transfer occurs by bulk flow, and the amount of the chemical itself crossing the boundary can be described as a chemical intake rate. The chemical

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[3]The National Research Council's 1983 report *Risk Assessment in the Federal Government: Managing the Process* often addresses the output of an exposure assessment as an exposure or a dose (NRC 1983, pp. 32, 35-36).

[4]These guidelines use the term *internal dose* to refer to the amount of a chemical absorbed across the exchange boundaries, such as the skin, lung, or gastrointestinal tract. The term *absorbed dose* is often used synonymously for internal dose, although the connotation for the term absorbed dose seems to be more related to a specific boundary (the amount absorbed across a membrane in an experiment, for example), while the term internal dose seems to connote a more general sense of the amount absorbed across one or more specific sites. For the purpose of these guidelines, the term internal dose is used for both connotations. The term internal dose as used here is also consistent with how it is generally applied to a discussion of biomarkers (NRC, 1989a). It is also one of the terms used in epidemiology (NRC, 1985).

intake rate is the amount of chemical crossing the outer boundary per unit time, and is the product of the exposure concentration times the ingestion or inhalation rate. Ingestion and inhalation rates are the amount of the carrier medium crossing the boundary per unit time, such as m^3 air breathed/hour, kg food ingested/day, or liters of water consumed/day. Ingestion or inhalation rates typically are not constant over time, but often can be observed to vary within known limits.[5]

The second process by which a chemical can cross the boundary from outside to inside the body is uptake. Uptake involves absorption of the chemical through the skin or other exposed tissue such as the eye. Although the chemical is often contained in a carrier medium, the medium itself typically is not absorbed at the same rate as the chemical, so estimates of the amount of the chemical crossing the boundary cannot be made in the same way as for intake (see Section 2.1.3). Dermal absorption is an example of direct uptake across the outer boundary of the body.[6] A chemical uptake rate is the amount of chemical absorbed per unit time. In this process, mass transfer occurs by diffusion, so uptake can depend on the concentration gradient across the boundary, permeability of the barrier, and other factors. Chemical uptake rates can be expressed as a function of the exposure concentration, permeability coefficient, and surface area exposed, or as a flux (see Section 2.1.4).

The conceptual process of contact, then entry and absorption, can be used to derive the equations for exposure and dose for all routes of exposure.

2.1.1. Exposure

The condition of a chemical contacting the outer boundary of a human is exposure. Most of the time, the chemical is contained in air, water, soil, a product, or a transport or carrier medium; the chemical concentration at the point of contact is the exposure concentration. Exposure over a period of time can be represented by a time-dependent profile of the exposure concentration. The area under the curve of this profile is the magnitude of the exposure, in concentration-time units (Lioy, 1990; NRC, 1990):

$$E = \int_{t_1}^{t_2} C(t)\, dt \qquad (2\text{-}1)$$

[5]Ingestion of food or water is an intermittent rather than continuous process, and can be expressed as (amount of medium per event) × (events per unit clock or calendar time) [the frequency of contact]; (e.g., 250 mL of water/glass of water ingested × 8 glasses of water ingested/day).

[6]Uptake through the lung, gastrointestinal tract, or other internal barriers also can occur following intake through ingestion or inhalation.

where E is the magnitude of exposure, C(t) is the exposure concentration as a function of time, and t is time, $t_2 - t_1$ being the exposure duration (ED). If ED is a continuous period of time (e.g., a day, week, year, etc.), then C(t) may be zero during part of this time.[7] Integrated exposures are done typically for a single individual, a specific chemical, and a particular pathway or exposure route over a given time period.[8]

The integrated exposures for a number of different individuals (a population or population segment, for example), may then be displayed in a histogram or curve (usually, with integrated exposure increasing along the abscissa or x-axis, and the number of individuals at that integrated exposure increasing along the ordinate or y-axis). This histogram or curve is a presentation of an exposure distribution for that population or population segment. The utility of both individual exposure profiles and population exposure distributions is discussed in Section 2.3.

2.1.2. Applied Dose and Potential Dose

Applied dose is the amount of a chemical at the absorption barrier (skin, lung, gastrointestinal tract) available for absorption. It is useful to know the applied dose if a relationship can be established between applied dose and internal dose, a relationship that can sometimes be established experimentally. Usually, it is very difficult to measure the applied dose directly, as many of the absorption barriers are internal to the human and are not localized in such a way to make measurement easy. An approximation of applied dose can be made, however, using the concept of potential dose[9] (Lioy, 1990; NRC, 1990).

Potential dose is simply the amount of the chemical ingested, inhaled, or in material applied to the skin. It is a useful term or concept for those instances in which there is exposure

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[7]*Contact time* (CT) is that part of the exposure duration where C(t) does not equal zero; that is, the actual time periods (events, episodes) during which actual exposure is taking place. The *exposure duration* as defined here, on the other hand, is a time interval of interest for assessment purposes during which exposure occurs, either continuously or intermittently.

[8]An *exposure pathway* is the course a chemical takes from its source to the person being contacted. An *exposure route* is the particular means of entry into the body, e.g., inhalation, ingestion, or dermal absorption.

[9]*Potential dose* is the potential amount of the chemical that could be absorbed if it were 100% bioavailable. Note, however, that this does not imply that 100% bioavailability or 100% absorption is assumed when using potential dose. The equations and discussion in this chapter use potential dose as a measurable quantity that can then be converted to applied or absorbed dose by the use of the appropriate factors. Potential dose is a general term referring to any of the exposure routes. The terms respiratory dose, oral dose, or dermal dose are sometimes used to refer to the route-specific potential doses.

to a discrete amount of chemical or transport medium, such as eating a certain amount of food or applying a certain amount of material to the skin.[10]

The potential dose for ingestion and inhalation is analogous to the administered dose in a dose-response experiment. Human exposure to environmental chemicals is generally inadvertent rather than administered, so in these Guidelines it is termed potential dose rather than administered dose. Potential dose can be used for dose-response relationships based on administered dose.

For the dermal route, potential dose is the amount of chemical applied, or the amount of chemical in the medium applied, for example as a small amount of particulate deposited on the skin. Note that as all of the chemical in the particulate is not contacting the skin, this differs from exposure (the concentration in the particulate times the time of contact) and applied dose (the amount in the layer actually touching the skin).

The applied dose, or the amount that reaches the exchange boundaries of the skin, lung, or gastrointestinal tract, may often be less than the potential dose if the material is only partly bioavailable. Where data on bioavailability are known, adjustments to the potential dose to convert it to applied dose and internal dose may be made.[11]

2.1.3. Internal Dose

The amount of a chemical that has been absorbed and is available for interaction with biologically significant receptors is called the internal dose. Once absorbed, the chemical can undergo metabolism, storage, excretion, or transport within the body. The amount transported to an individual organ, tissue, or fluid of interest is termed the delivered dose. The delivered dose may be only a small part of the total internal dose. The biologically effective dose, or the amount that actually reaches cells, sites, or membranes where adverse effects occur (NRC, 1990, p. 29), may only be a part of the delivered dose, but it is obviously the crucial part. Currently, most risk assessments dealing with environmental chemicals (as opposed to pharmaceutical assessments) use dose-response relationships based on potential (administered) dose or internal

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[10]It is not useful to calculate potential doses in cases where there is partial or total immersion in a fluid such as air or water. In these cases, it is more useful to describe the situation in terms of exposure (concentration of the chemical in the medium times the time of contact) or absorbed dose. For cases such as contact with water in a swimming pool, the person is not really exposed to the entire mass of the chemical that would be described by a potential dose. Nor is it useful to calculate dermal applied doses because the boundary layer is being constantly renewed. The use of alternate ways to calculate a dose that might occur while swimming is discussed in Section 2.1.4.2, in conjunction with Equations 2-7 and 2-8.

[11]This may be done by adding a bioavailability factor (range: 0 to 1) to the dose equation. The bioavailability factor would then take into account the ability of the chemical to be extracted from the matrix, absorption through the exchange boundary, and any other losses between ingestion and contact with the lung or gastrointestinal tract. When no data or information are available to indicate otherwise, the bioavailability factor is usually assumed to be 1.

dose, since the pharmacokinetics necessary to base relationships on the delivered dose or biologically effective doses are not available for most chemicals. This may change in the future, as more becomes known about the pharmacokinetics of environmental chemicals.

Doses are often presented as dose rates, or the amount of a chemical dose (applied or internal) per unit time (e.g., mg/day), or as dose rates on a per-unit-body-weight basis (e.g., mg/kg/day).

Distributions of individual doses within a population or population segment may be displayed in a histogram or curve analogous to the exposure distributions described in Section 2.1.1. The utility of individual dose profiles, as well as the utility of population distributions of dose are described more fully in Section 2.3.

2.1.4. Exposure and Dose Relationships

Depending on the use of the exposure assessment, estimates of exposure and dose in various forms may be required.

- Exposure concentrations are useful when comparing peak exposures to levels of concern such as short-term exposure limits (STELs). They are typically expressed in units such as $\mu g/m^3$, mg/m^3, mg/kg, $\mu g/L$, mg/L, ppb, or ppm.
- Exposure or dose profiles describe the exposure concentration or dose as a function of time. Concentration and time are used to depict exposure, while amount and time characterize dose; graphical or tabular presentations may be used for either type of profile.

Such profiles are very important for use in risk assessment where the severity of effect is dependent on the pattern by which the exposure occurs rather than the total (integrated) exposure. For example, a developmental toxin may only produce effects if exposure occurs during a particular stage of development. Similarly, a single acute exposure to very high contaminant levels may induce adverse effects even if the average exposure is much lower than apparent no-effect levels. Such profiles will become increasingly important as biologically based dose-response models become available.

- Integrated exposures are useful when a total exposure for a particular route (i.e., the total for various pathways leading to exposure via the same route) is needed. Units of integrated exposure are concentration times time. The integrated exposure is the total area under the curve of the exposure profile (Equation 2-1). Note that an exposure profile (a picture of exposure concentration over time) contains more information than an integrated exposure (a number), including the duration and periodicity of exposure, the peak exposure, and the shape of the area under the time-concentration curve.

- Time-weighted averages are widely used in exposure assessments, especially as part of a carcinogen risk assessment. A time-weighted average exposure concentration (units of concentration) is the integrated exposure divided by the period where exposure occurs, and is useful in some of the equations discussed below in estimating dose. A time-weighted average dose rate is the total dose divided by the time period of dosing, usually expressed in units of mass per unit time, or mass/time normalized to body weight (e.g., mg/kg/day). Time-weighted average dose rates such as the lifetime average daily dose (LADD) are often used in dose-response equations to estimate effects or risk.[12]

The discussion in the next three sections focuses on exposure via inhalation, oral intake, and dermal absorption. Other exposure routes are possible, however, including direct introduction into the bloodstream via injection or transfusion, contamination of exposed lesions, placental transfer, or use of suppositories. The exposures and doses for these routes can be calculated in a similar manner, depending on whether an intake or uptake process is involved.

Although equations for calculating exposure, dose, and their various averages are in widespread use in exposure assessment, the assessor should consider the implications of the assumptions used to derive the equations. Simplifying assumptions used in deriving the equations may mean that variations in exposure concentration, ingestion or inhalation rate, permeability coefficient, surface area exposed, and absorption fraction can introduce error into the estimate of dose if average values are used, and this must be considered in the evaluation of uncertainty (Section 6).

2.1.4.1. *Calculating Potential Dose for Intake Processes*

The general equation for potential dose for intake processes, e.g., inhalation and ingestion (see Figure 1 for illustration of various exposures and doses) is simply the integration of the chemical intake rate (concentration of the chemical in the medium times the intake rate of the medium, C times IR) over time:

$$D_{pot} = \int_{t_1}^{t_2} C(t)\ IR(t)\ dt \qquad (2\text{-}2)$$

---

[12]Current carcinogen risk models, such as the linearized multistage procedure and other linear nonthreshold models, use lifetime exposures to develop the dose-response relationships, and therefore use lifetime time-weighted average exposures to estimate risks. Within the range of linearity for risk, this procedure effectively treats exposures and doses as a series of "units," with each unit of dose being equal to any other unit of dose in terms of risk potential without respect to prior exposure or dose patterns. Current research in the field of dose-response modeling is focusing on biologically based dose-response models which may take into account the effects of the exposure or dose patterns, making use of all of the information in an exposure or dose profile. For a more indepth discussion on the implications of the use of time-weighted averages, see Atherley (1985).

where D_{pot} is potential dose and IR(t) is the ingestion or inhalation rate.

The quantity $t_2 - t_1$, as before, represents the period of time over which exposure is being examined, or the exposure duration (ED). The exposure duration may contain times where the chemical is in contact with the person, and also times when C(t) is zero. Contact time represents the actual time period where the chemical is in contact with the person. For cases such as ingestion, where actual contact with food or water is intermittent, and consequently the actual contact time may be small, the intake rate is usually expressed in terms of a frequency of events (e.g., 8 glasses of water consumed per day) times the intake per event (e.g., 250 mL of water/glass of water consumed). Intermittent air exposures (e.g., 8 hours exposed/day times one cubic meter of air inhaled/hour) can also be expressed easily using exposure duration rather than contact time. Hereafter, the term exposure duration will be used in the examples below to refer to the term $t_2 - t_1$, since it occurs frequently in exposure assessments and it is often easier to use.

Equation 2-2 can also be expressed in discrete form as a summation of the doses received during various events I:

$$D_{pot} = \sum_i C_i \cdot IR_i \cdot ED_i \qquad (2\text{-}3)$$

where ED_i is the exposure duration for event I. If C and IR are nearly constant (which is a good approximation if the contact time is very short), Equation 2-3 becomes:

$$D_{pot} = \bar{C} \cdot \bar{IR} \cdot ED \qquad (2\text{-}4)$$

where ED is the sum of the exposure durations for all events, and $\bar{C}$ and $\bar{IR}$ are the average values for these parameters. Equation 2-4 will not necessarily hold in cases where C and IR vary considerably. In those cases, Equation 2-3 can be used if the exposure can be broken out into segments where C and IR are approximately constant. If even this condition cannot be met, Equation 2-2 may be used.

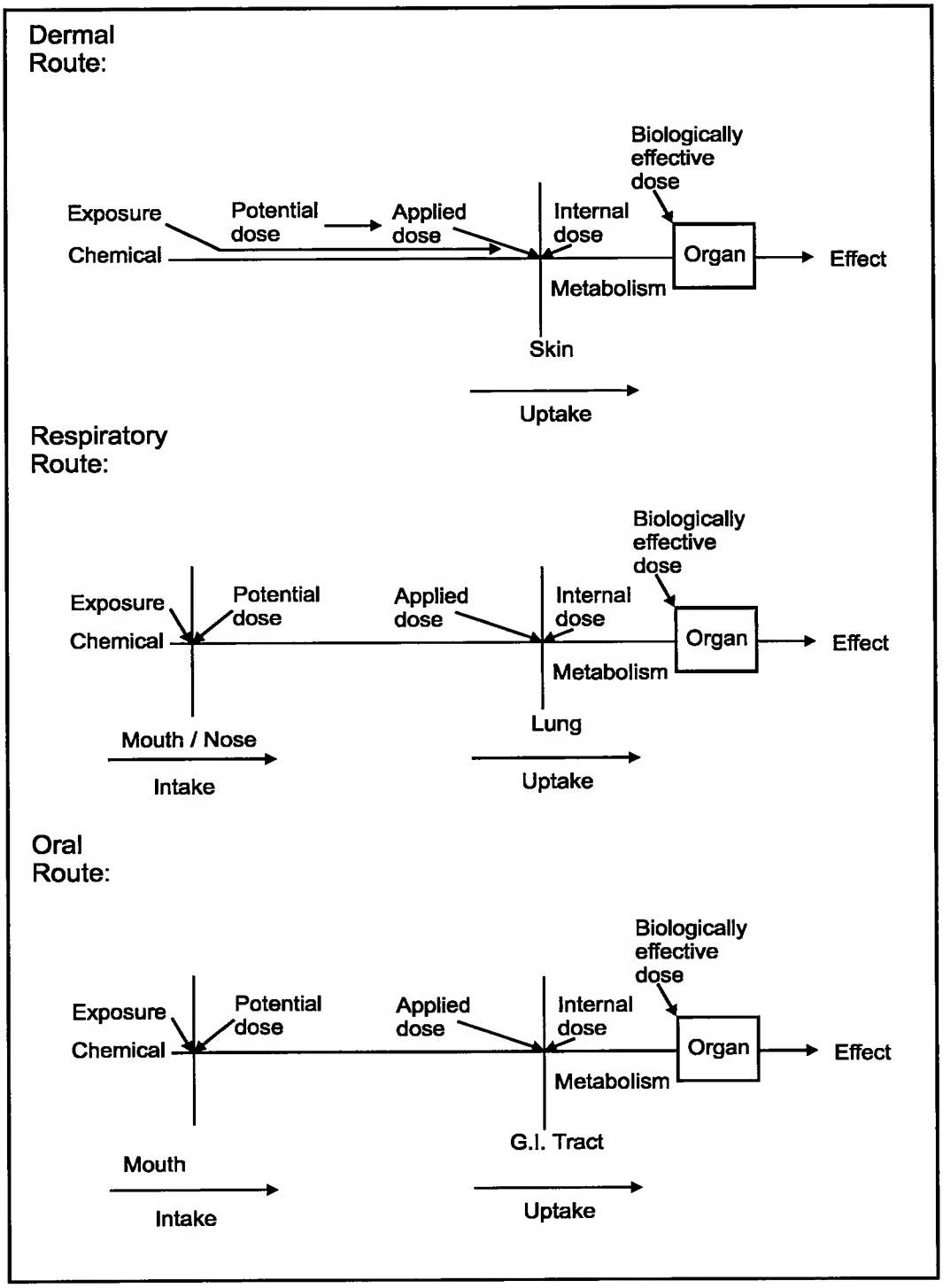

Figure 1.

Schematic of dose and exposure.

For risk assessment purposes, estimates of dose should be expressed in a manner that can be compared with available dose-response data. Frequently, dose-response relationships are based on potential dose (called administered dose in animal studies), although dose-response relationships are sometimes based on internal dose.

Doses may be expressed in several different ways. Solving Equations 2-2, 2-3, or 2-4, for example, gives a total dose accumulated over the time in question. The dose per unit time is the dose rate, which has units of mass/time (e.g., mg/day). Because intake and uptake can vary, dose rate is not necessarily constant. An average dose rate over a period of time is a useful number for many risk assessments.

Exposure assessments should take into account the time scale related to the biological response studied unless the assessment is intended to provide data on the range of biological responses (NRC, 1990, p. 28). For many noncancer effects, risk assessments consider the period of time over which the exposure occurred, and often, if there are no excursions in exposure that would lead to acute effects, average exposures or doses over the period of exposure are sufficient for the assessment. These averages are often in the form of average daily doses (ADDs).

An ADD can be calculated from Equation 2-2 by averaging D_{pot} over body weight and an averaging time, provided the dosing pattern is known so the integral can be solved. It is unusual to have such data for human exposure and intake over extended periods of time, so some simplifying assumptions are commonly used. Using Equation 2-4 instead of 2-2 or 2-3 involves making steady-state assumptions about C and IR, but this makes the equation for ADD easier to solve.[13] For intake processes, then, using Equation 2-4, this becomes:

$$ADD_{pot} = [\bar{C} \cdot \bar{IR} \cdot ED] \ / \ [BW \cdot AT] \qquad (2\text{-}5)$$

where ADD_{pot} is the average daily potential dose, BW is body weight, and AT is the time period over which the dose is averaged (converted to days). As with Equation 2-4, the exposure concentration $\bar{C}$ is best expressed as an estimate of the arithmetic mean regardless of the distribution of the data. Again, using average values for C and IR in Equation 2-5 assumes that C and IR are approximately constant.

For effects such as cancer, where the biological response is usually described in terms of lifetime probabilities, even though exposure does not occur over the entire lifetime, doses are often presented as lifetime average daily doses (LADDs). The LADD takes the form of Equation 2-5, with lifetime (LT) replacing the averaging time (AT):

---

[13]The assessor should keep in mind that this steady state assumption has been made when using Equation 2-5, and should be able to discuss what effect using average values for C, IR, and ED has on the resulting estimate.

$$ADD_{pot} = [\ \bar{C} \cdot \bar{IR} \cdot ED] \ / \ [BW \cdot LT] \quad (2\text{-}6)$$

The LADD is a very common term used in carcinogen risk assessment where linear nonthreshold models are employed.

2.1.4.2. *Calculating Internal Dose for Uptake Processes (Especially via the Dermal Route)*

For absorption processes, there are two methods generally in use for calculating internal dose. The first, commonly used for dermal absorption from a liquid where at least partial immersion occurs, is derived from the equation for internal dose, D_{int}, which is analogous to Equation 2-2 except that the chemical uptake rate ($C \cdot K_p \cdot SA$) replaces the chemical intake rate ($C \cdot IR$). Thus,

$$D_{int} = \int_{t_1}^{t_2} C(t) \cdot K_p \cdot SA(t)\ dt \quad (2\text{-}7)$$

where K_p is the permeability coefficient, and SA is the surface area exposed. Both C and SA will vary over time, and although K_p may not vary over time, it may vary over different parts of the body. Unlike the intake processes, where the rate of the carrier medium crossing the boundary can be observed or measured, the carrier may or may not cross the absorption barrier; the equations must be in terms of the chemical itself crossing. The flow of the chemical across the barrier (or flux, J) is not directly measurable, and is dependent on many factors including the nature of the chemical, the nature of the barrier, active transport versus passive diffusion processes, and the concentration of the chemical contacting the barrier. The relationship between the flux and the exposure concentration[14] is usually expressed as a permeability coefficient, K_p, which is experimentally measurable.[15] The internal dose that is analogous to the potential dose in Equation 2-4 would be:

$$D_{int} = \bar{C} \cdot K_p \cdot \bar{SA} \cdot ED \quad (2\text{-}8)$$

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[14]This relationship is described by Fick's Law, where $J = K_p \cdot C$ where C represents the steady-state concentration of the chemical, J is the steady-state flux, and K_p is the permeability coefficient.

[15]The permeability coefficient, K_p, can be experimentally calculated for a chemical and a particular barrier (e.g., skin type) by observing the flux rate *in vitro* (typical units: mg chemical crossing/sec-cm^2), and dividing it by the concentration of the chemical in the medium in contact with the barrier (typical units: mg chemical/cm^3). This allows the relationship between bulk concentration and the crossing of the chemical itself to be made. K_p has the advantage of being fairly constant over a range of concentrations and can be used for concentrations other than the one used in the experiment. The chemical uptake rate, relating the crossing of the barrier of the chemical itself in terms of the bulk concentration, then becomes C times K_p times the surface area exposed (SA).

where $\bar{SA}$ is the average surface area exposed and the ADD_{int} (average daily internal dose) becomes:

$$ADD_{int} = [\ \bar{C} \cdot K_p \cdot \bar{SA} \cdot ED\ ] / [\ BW \cdot AT\ ] \qquad (2\text{-}9)$$

(The corresponding $LADD_{int}$ would be obtained by substituting LT for AT.) This is the method to use when calculating internal dose for a swimmer. The total body surface area (SA) is assumed to be exposed to a layer of water with an average chemical concentration $\bar{C}$ for a period of time (ED). It is not necessary to know the mass of the chemical that comes in contact with the skin. The assumptions necessary in going from Equation 2-7 to Equation 2-9 are comparable to those made in deriving Equation 2-5. Recall that both C and SA will vary over time, and K_p may not be constant over different parts of the body. If the assumption used to derive Equation 2-5 (that these variables are nearly constant) does not hold, a different form of the equation having several terms must be used.

The second method of calculating internal dose uses empirical observations or estimates of the rate that a chemical is absorbed when a dose is administered or applied. It is useful when a small or known amount of material (such as a particulate) or a chemical (such as a pesticide) contacts the skin. The potential dose of a chemical to the skin, D_{pot}, can often be calculated from knowing the concentration (C) and the amount of carrier medium applied (M_{medium}), either as a whole or on a unit surface area basis. For example, potential dose from dermal contact with soil can be calculated using the following equation:

$$D_{pot} = \bar{C} \cdot M_{medium} = \bar{C} \cdot F_{adh} \cdot \bar{SA} \cdot ED \qquad (2\text{-}10)$$

where D_{pot} is potential dose, M_{medium} is amount of soil applied, and F_{adh} is the adherence factor for soil (the amount of soil applied to and adhering to the skin on a unit surface area per unit time).

The relationship between potential dose and applied dose for dermal exposures is that potential dose includes the amount of the chemical in the total amount of medium contacting the skin, e.g., the amount of chemical in the soil whether or not all the chemical itself ever comes in direct contact, and applied dose includes only that amount of the chemical which actually directly touches the skin. Theoretically, the relationship between the applied dose (D_{app}) and the internal (or absorbed) dose (D_{int}) can be thought of as:

$$D_{int} = D_{app} \int_{t_1}^{t_2} f(t)\ dt \qquad (2\text{-}11)$$

where f(t) is a complicated nonlinear absorption function, usually not measurable, having the dimensions of mass absorbed per mass applied per unit time. The absorption function will vary due to a number of factors (concentration gradient of chemical, carrier medium, type of skin, skin moisture, skin condition, etc.). If f(t) could be integrated over time from the start of exposure until time T, it would yield the absorption fraction, AF, which is the fraction of the applied dose that is absorbed after time T. The absorption fraction is a cumulative number and can increase with time to a possible maximum of 1 (or 100% absorption), but due to competing processes may reach steady state long before reaching 100% absorption. Equation 2-11 then becomes:

$$D_{int} = D_{app} \cdot AF \tag{2-12}$$

where AF is the absorption fraction in units of mass absorbed/mass applied (dimensionless).

If one assumes that all the chemical contained in the bulk material will eventually come in contact with the skin, then D_{app} equals D_{pot} and using Equation 2-12, the D_{int} equation becomes:

$$D_{int} = D_{pot} \cdot AF \tag{2-13}$$

and (using Equations 2-9 and 2-10) consequently:

$$ADD_{int} = [\ \bar{C} \cdot M_{medium} \cdot AF\ ] / [\ BW \cdot AT\ ] \tag{2-14}$$

where M_{medium} is the mass of the bulk material applied to the skin. For reasons explained below, this approximation will by no means always give credible results. The key is whether all the chemical contained in the bulk medium can actually contact the skin. Although with certain liquids or small amounts of material, the applied dose may be approximately equal to the potential dose, in cases where there is contact with more than a minimal amount of soil, there is research that indicates that using this approximation may cause serious error (Yang et al., 1989). When this approximation does not hold, the assessor must make assumptions about how much of the bulk material actually contacts the skin, or use the first method of estimating internal dose outlined above.

Unfortunately, almost no data are available concerning the relationship between potential dose and applied dose for dermal exposures. Experimental data on absorption fractions derived for soil commonly use potential dose rather than applied dose, which may make the experimental data at least in part dependent on experimental conditions such as how much soil was applied. If

the exposure assessment conditions are similar to those in the experiment, this would not usually introduce much error, but if the conditions vary widely, the error introduced may be difficult to determine.

As a practical matter, estimates of absorption fraction are often crude approximations and may be difficult to refine even if some data from experiments are available in the published literature. Typically, absorption experiments report results as an absorption fraction after a given time (e.g., 50% after 24 hours). Since absorption fraction is a function of several variables such as skin temperature, pH, moisture content, and exposed surface area, as well as characteristics of the matrix in which the chemical occurs (e.g., soil particle size distribution, organic matter content, and moisture content), it is often difficult to make comparisons between experimental data and conditions being considered for an assessment.

With single data points, it may not be clear whether the experiment reached steady state. If several data points are available from different times in the experiment, a plot of absorption fraction vs. time may be instructive. For chemicals where data are available for steady-state conditions, the steady-state value will probably be a good approximation to use in assessments where exposure duration is at least this long, provided the conditions in the experiment are similar to those of the case being assessed. Assessors should be very cautious in applying absorption fractions for moderately absorbed chemicals (where observed experimental absorption fractions are not in the steady-state part of the cumulative curve), or in using experimental data for estimates of absorption over a much shorter duration than in the experiment.

In almost all cases, the absorption fraction method of estimating internal dose from applied dose gives only an approximation of the internal dose. The interested reader is referred to U.S. EPA (1992b) for more thorough guidance on dermal exposure assessment.

2.1.4.3. *Calculating Internal Dose for Intake Processes (Especially via Respiratory and Oral Routes)*

Chemicals in air, food, or drinking water normally enter the body through intake processes, then are subsequently absorbed through internal uptake processes in the lung or gastrointestinal tract. Sometimes it is necessary to estimate resulting internal dose, D_{int}, after intake. In addition, if enough is known about the pharmacokinetics of the chemical to make addition of doses across routes a meaningful exercise, the doses must be added as internal dose, not applied dose, potential dose, or exposure.

Theoretically, one could calculate D_{int} in these cases by using an equation similar to Equation 2-7; but C in that equation would become the concentration of the chemical in the lung or gastrointestinal tract, SA would be the internal surface area involved, and K_p would be the

permeability coefficient of the lung or gastrointestinal tract lining. Although data from the pharmaceutical field may be helpful in determining, for example, internal surface areas, all of the data mentioned above are not known, nor are they measurable with current instrumentation.

Because Equations 2-2 through 2-4 estimate the potential dose D_{pot}, which is the amount ingested or inhaled, and Equations 2-11 and 2-12 provide relationships between the applied dose (D_{app}) and internal dose (D_{int}), all that is necessary is a relationship between potential dose and applied dose for intake processes. Again, data on this topic are virtually nonexistent, so a common assumption is that for intake processes, the potential dose equals the applied dose. Although arguments can be made that this assumption is likely to be more nearly accurate than for the case of soil contact, the validity of this assumption is unknown at this point. Essentially, the assumption of equality means that whatever is eaten, drunk, or inhaled touches an absorption barrier inside the person.

Assuming potential dose and applied dose are approximately equal, the internal dose after intake can be estimated by combining Equations 2-2 or 2-3 and 2-10 or 2-11. Using Equations 2-3 and 2-11, this becomes:

$$D_{int} = D_{app} \cdot AF \approx D_{pot} \cdot AF = \bar{C} \cdot \bar{IR} \cdot ED \cdot AF \qquad (2\text{-}15)$$

The ADD_{int} for the two-step intake/uptake process becomes:

$$ADD_{int} \approx ADD_{pot} \cdot AF = [\ \bar{C} \cdot \bar{IR} \cdot ED \cdot AF\ ] / [\ BW \cdot AT\ ] \qquad (2\text{-}16)$$

Using average values for $\bar{C}$ and $\bar{IR}$ in Equations 2-15 and 2-16 involves the same assumptions and cautions as were discussed in deriving the ADD and LADD equations in the previous two sections, and of course, the same cautions apply to the use of the absorption fraction as were outlined in Section 2.1.4.2.

2.1.5. Summary of Exposure and Dose Terms With Example Units

Table 1 provides a summary of the exposure and dose terms discussed in Section 2.1, along with examples of units commonly used.

2.2. APPROACHES TO QUANTIFICATION OF EXPOSURE

Although exposure assessments are done for a variety of reasons (see Section 3), the quantitative exposure estimate can be approached from three different ways[16]:

1. The exposure can be measured at the point of contact (the outer boundary of the body) while it is taking place, measuring both exposure concentration and time of contact and integrating them (point-of-contact measurement),
2. The exposure can be estimated by separately evaluating the exposure concentration and the time of contact, then combining this information (scenario evaluation),
3. The exposure can be estimated from dose, which in turn can be reconstructed through internal indicators (biomarkers,[17] body burden, excretion levels, etc.) after the exposure has taken place (reconstruction).

These three approaches to quantification of exposure (or dose) are independent, as each is based on different data. The independence of the three methods is a useful concept in verifying or validating results. Each of the three has strengths and weaknesses; using them in combination can considerably strengthen the credibility of an exposure or risk assessment. Sections 2.2.1 through 2.2.3 briefly describe some of the strengths and weaknesses of each approach.

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[16]These three ways are approaches for arriving at a quantitative estimate of exposure. Sometimes the approaches to assessing exposure are described in terms of "direct measures" and "indirect measures" of exposure (e.g., NRC, 1990). Measurements that actually involve sampling on or within a person, for example, use of personal monitors and biomarkers, are termed "direct measures" of exposure. Use of models, microenvironmental measurements, and questionnaires, where measurements do not actually involve personal measurements, are termed "indirect measures" of exposure. The direct/indirect nomenclature focuses on the type of measurements being made; the scenario evaluation/point-of-contact/reconstruction nomenclature focuses on how the data are used to develop the dose estimate. The three-term nomenclature is used in these guidelines to highlight the point that three independent estimates of dose can be developed.

[17]Biomarkers can be used to study exposure, effects, or susceptibility. The discussion of biomarkers in these guidelines is limited to their use in indicating exposure.

Table 1. Explanation of exposure and dose terms

Term	Refers to	Generic units	Specific example units	
Exposure	Contact of chemical with outer boundary of a person, e.g., skin, nose, mouth.	concentration x time	**Dermal:**	(mg chem/L water) • (hrs of contact) (mg chem/kg soil) • (hrs of contact)
			Respiratory:	(ppm chem in air) • (hrs of contact) ($\mu g/m^3$ air) • (days of contact)
			Oral:	(mg chem/L water) • (min of contact) (mg chem/kg food) • (min of contact)
Potential dose	Amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin.	mass of the chemical: Dose rate is mass of the chemical/time; the dose rate is sometimes normalized to body weight: mass of chemical/unit body weight • time	**Dermal:**	(mg chem/kg soil) • (kg soil on skin) = mg chem in soil applied to skin
			Respiratory:	(μg chem/m^3 air) • (m^3 air breathed/min) • (min exposed) = μg chemical in air breathed
			Oral:	(mg chem/L water) • (L water consumed/day) • days exposed = mg chemical ingested in water (also dose rate: mg/day)
Applied dose	Amount of chemical in contact with the primary absorption boundaries (e.g., skin, lungs, gastrointestinal tract) and available for absorption	as above	**Dermal:**	(mg chem/kg soil) • (kg soil directly touching skin) • (% of chem in soil actually touching skin) = mg chem actually touching skin
			Respiratory:	(μg chem/m^3 air) • (m^3 air directly touching lung) • (% of chemical actually touching lung) = mg chemical actually touching lung absorption barrier
			Oral:	(mg chem/kg food) • (kg food consumed/day) • (% of chemical touching g.i. tract) = mg chemical actually touching g.i. tract absorption barrier (also absorbed dose rate: mg/day) chemical available to organ or cell (dose rate: mg chemical available to organ/day)

Table 1. Explanation of exposure and dose terms (continued)

Term	Refers to	Generic units	Specific example units	
Internal (absorbed) dose	The amount of a chemical penetrating across an absorption barrier or exchange boundary via either physical or biological processes.	as above	**Dermal:**	mg chemical absorbed through skin mg chemical absorbed via lung
			Respiratory:	mg chemical absorbed via g.i. tract
			Oral:	(dose rate: mg chemical absorbed/day or mg/kg • day)
Delivered dose	Amount of chemical available for interaction with any particular organ or cell.	as above		mg chemical available to organ or cell (dose rate: mg chemical available to organ/day)

2.2.1. Measurement of Exposure at the Point of Contact

Point-of-contact exposure measurement evaluates the exposure as it occurs, by measuring the chemical concentrations at the interface between the person and the environment as a function of time, resulting in an exposure profile. The best known example of the point-of-contact measurement is the radiation dosimeter. This small badge-like device measures exposure to radiation as it occurs and provides an integrated estimate of exposure for the period of time over which the measurement has been taken. Another example is the Total Exposure Assessment Methodology (TEAM) studies (U.S. EPA, 1987a) conducted by the EPA. In the TEAM studies, a small pump with a collector and absorbent was attached to a person's clothing to measure his or her exposure to airborne solvents or other pollutants as it occurred. A third example is the carbon monoxide (CO) point-of-contact measurement studies where subjects carried a small CO measuring device for several days (U.S. EPA, 1984a). Dermal patch studies and duplicate meal studies are also point-of-contact measurement studies. In all of these examples, the measurements are taken at the interface between the person and the environment while exposure is occurring. Use of these data for estimating exposures or doses for periods that differ from those for which the data are collected (e.g., for estimates of lifetime exposures) will require some assumptions, as discussed in Section 5.3.1.

The strength of this method is that it measures exposure directly, and providing that the measurement devices are accurate, is likely to give the most accurate exposure value for the period of time over which the measurement was taken. It is often expensive, however, and measurement devices and techniques do not currently exist for all chemicals. This method may also require assumptions to be made concerning the relationship between short-term sampling and long-term exposures, if appropriate. This method is also not source-specific, a limitation when particular sources will need to be addressed by risk managers.

2.2.2. Estimates of Exposure from Scenario Evaluation

In exposure scenario evaluation, the assessor attempts to determine the concentrations of chemicals in a medium or location and link this information with the time that individuals or populations contact the chemical. The set of assumptions about how this contact takes place is an exposure scenario. In evaluating exposure scenarios, the assessor usually characterizes the chemical concentration and the time of contact separately. This may be done for a series of events, e.g., by using Equation 2-3, or using a steady-state approximation, e.g., using Equation 2-4.

The goal of chemical concentration characterization is to develop estimates of exposure concentration. This is typically accomplished indirectly by measuring, modeling, or using existing data on concentrations in the bulk media, rather than at the point of contact. Assuming

the concentration in the bulk medium is the same as the exposure concentration is a clear source of potential error in the exposure estimate and must be discussed in the uncertainty analysis. Generally, the closer the medium can be measured to the point of contact (in both space and time), the less uncertainty there is in the characterization of exposure concentration.

The goal of characterizing time of contact is to identify who is exposed and to develop estimates of the frequency and duration of exposure. Like chemical concentration characterization, this is usually done indirectly by use of demographic data, survey statistics, behavior observation, activity diaries, activity models, or, in the absence of more substantive information, assumptions about behavior.

The chemical concentration and population characterizations are ultimately combined in an exposure scenario, and there are various ways to accomplish this. One of the major problems in evaluating dose equations such as Equations 2-4 through 2-6 is that the limiting assumptions or boundary conditions used to derive them (e.g., steady-state assumptions; see Section 2.1.4) do not always hold true. Two major approaches to this problem are (1) to evaluate the exposure or dose equation under conditions where the limiting assumptions do hold true, or (2) to deal with the uncertainty caused by the divergence from the boundary conditions. As an example of the first way, the microenvironment method, usually used for evaluating air exposures, evaluates segments of time and location where the assumption of constant concentration is approximately true, then sums over all such time segments for a total exposure for the respiratory route, effectively removing some of the boundary conditions by falling back to the more general Equation 2-3. While estimates of exposure concentration and time-of-contact are still derived indirectly by this method, the concentration and time-of-contact estimates can be measured for each microenvironment. This avoids much of the error due to using average values in cases where concentration varies widely along with time of contact.[18]

As examples of the second approach, there are various tools used to describe uncertainty caused by parameter variation, such as Monte Carlo analysis (see Section 5). Section 6 discusses some of these techniques in more detail.

One strength of the scenario evaluation approach is that it is usually the least expensive method of the three. Also, it is particularly suited to analysis of the risk consequences of proposed actions. It is both a strength and a weakness of scenario development that the

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[18]This technique still may not deal effectively with the problem of short-term "peak concentrations" exceeding some threshold leading to an acute effect. Even the averaging process used in a microenvironment may miss significant concentration spikes and average them out to lower concentrations which are apparently less toxicologically significant. A similar problem exists when evaluating sources; a "peak release" of a toxic chemical for a short time may cause serious acute effects, even though the average concentration over a longer period of time might not indicate serious chronic effects.

evaluation can be performed with little or no data; it is a technique that is best used when some knowledge exists about the soundness, validity, and uncertainty of the underlying assumptions.

2.2.3. Exposure Estimation by Reconstruction of Internal Dose

Exposure can also be estimated after it has taken place. If a total dose is known, or can be reconstructed, and information about intake and uptake rates is available, an average past exposure rate can be estimated. Reconstruction of dose relies on measuring internal body indicators after exposure and intake and uptake have already occurred, and using these measurements to back-calculate dose. However, the data on body burden levels or biomarkers cannot be used directly unless a relationship can be established between these levels or biomarker indications and internal dose, and interfering reactions (e.g., metabolism of unrelated chemicals) can be accounted for or ruled out. Biological tissue or fluid measurements that reveal the presence of a chemical may indicate directly that an exposure has occurred, provided the chemical is not a metabolite of other chemicals.

Biological monitoring can be used to evaluate the amount of a chemical in the body by measuring one or more of the following items. Not all of these can be measured for every chemical:

- the concentration of the chemical itself in biological tissues or sera (blood, urine, breath, hair, adipose tissue, etc.),
- the concentration of the chemical's metabolite(s),
- the biological effect that occurs as a result of human exposure to the chemical (e.g., alkylated hemoglobin or changes in enzyme induction), or
- the amount of a chemical or its metabolites bound to target molecules.

The results of biomonitoring can be used to estimate chemical uptake during a specific interval if background levels do not mask the marker and the relationships between uptake and the marker selected are known. The time of sampling for biomarkers can be critical. Establishing a correlation between exposure and the measurement of the marker, including pharmacokinetics, can help optimize the sampling conditions.

The strengths of this method are that it demonstrates that exposure to and absorption of the chemical has actually taken place, and it theoretically can give a good indication of past exposure. The drawbacks are that it will not work for every chemical due to interferences or the reactive nature of the chemical, it has not been methodologically established for very many chemicals, data relating internal dose to exposure are needed, and it may be expensive.

2.3. RELATIONSHIPS OF EXPOSURE AND DOSE TO RISK

Exposure and dose information are often combined with exposure-response or dose-response relationships to estimate risk, the probability of an adverse effect occurring. There are a variety of risk models, with various mathematical relationships between risk and dose or (less frequently) exposure. A major function of the exposure assessment as part of a risk assessment is to provide the exposure or dose values, and their interpretations.

The exposure and dose information available will often allow estimates of individual risk or population risk, or both. Presentation of risks in a risk assessment involves more than merely a numerical value, however. Risks can be described or characterized in a number of different ways. This section discusses the relationships between exposure and dose and a series of risk descriptors.

In preparing exposure information for use in a risk assessment, the use of several descriptors, including descriptors of both individual and population risk, often provides more useful information to the risk manager than a single descriptor or risk value. Developing several descriptors may require the exposure assessor to analyze and evaluate the exposure and dose information in several different ways. The exposure assessor should be aware of the purpose, scope, and level of detail of the assessment (see Sections 3.1 through 3.3) before gathering data, since the types and amounts of data needed may differ. The questions that need to be addressed as a result of the purpose of the assessment determine the type of risk descriptors used in the assessment.

2.3.1. Individual Risk

Individual risk is risk borne by individual persons within a population. Risk assessments almost always deal with more than a single individual. Frequently, individual risks are calculated for some or all of the persons in the population being studied, and are then put into the context of where they fall in the distribution of risks for the entire population.

Descriptions of individual risk can take various forms, depending on the questions being addressed. For the risk manager, there are often key questions in mapping out a strategy for dealing with individual risk. For cancer (or when possible, noncancer) assessments, the risk manager may need answers to questions such as:

- Are individuals at risk from exposure to the substances under study? Although for substances, such as carcinogens, that are assumed to have no threshold, only a zero dose would result in no excess risk; for noncarcinogens, this question can often be addressed. In the case of the use of hazard indices, where exposures or doses are compared to a reference dose or some other acceptable level, the risk descriptor would be a statement based on the ratio between the dose incurred and the reference dose.

- To what risk levels are the persons at the highest risk subjected?
- Who are these people, what are they doing, where do they live, etc., and what might be putting them at this higher risk?
- Can people with a high degree of susceptibility be identified?
- What is the average individual risk?

In addressing these questions, risk descriptors may take any of several forms:

- an estimate of the probability that an individual in the high end of the distribution may suffer an adverse effect, along with an explanation (to the extent known) of the (exposure or susceptibility) factors which result in their being in the high end;
- an estimate of the probability that an individual at the average or median risk may suffer an adverse effect; or
- an estimate of the probability that an individual will suffer an adverse effect given a specific set of exposure circumstances.

Individuals at the high end of the risk distribution are often of interest to risk managers when considering various actions to mitigate risk. These individuals often are either more susceptible to the adverse health effect than others in the population or are highly exposed individuals, or both.

Higher susceptibility may be the result of a clear difference in the way the chemical is processed by the body, or it may be the result of being in the extreme part of the normal range in metabolism for a population. It may not always be possible to identify persons or subgroups who are more susceptible than the general population. If groups of individuals who have clearly different susceptibility characteristics can be identified, they can be treated as a separate subpopulation, and the risk assessment for this subgroup may require a different dose-response relationship from the one used for the general population. When highly susceptible individuals can be identified, but when a different dose-response relationship is not appropriate or feasible to develop, the risks for these individuals are usually treated as part of the variability of the general population.

Highly exposed individuals have been described in the literature using many different terms. Because of unclear definitions, terms such as maximum exposed individual,[19] worst case

[19]The uppermost portion of the high-end exposure range has generally been the target for terms such as "maximum exposed individual," although actual usage has varied.

exposure,[20] and reasonable worst case exposure[21] have sometimes been applied to a variety of *ad hoc* estimates with unclear target ranges. The term maximum exposed individual has often been used synonymously with worst case exposure, that is, to estimate the exposure of the individual with the highest actual or possible exposure. An accurate estimate of the exposure of the person in the distribution with the highest exposure is extremely difficult to develop; uncertainty in the estimate usually increases greatly as the more extreme ends of the distribution are approached. Even using techniques such as Monte Carlo simulations can result in high uncertainty about whether the estimate is within, or above, the actual exposure distribution.

For the purpose of these guidelines, a high end exposure estimate is a plausible estimate of the individual exposure for those persons at the upper end of an exposure distribution. The intent of this designation is to convey an estimate of exposures in the upper range of the distribution, but to avoid estimates that are beyond the true distribution. Conceptually, the high end of the distribution means above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest exposure. High-end dose estimates are described analogously.

The concept of the high-end exposure, as used in this guidance, is fundamentally different from terms such as worst case, in that the estimate is by definition intended to fall on the actual (or in the case of scenarios dealing with future exposures, probable) exposure distribution.

> Key Point: The primary objective when developing an estimate of high-end exposure or dose is to arrive at an estimate that will fall *within* the actual distribution, rather than *above* it. (Estimates above the distribution are bounding estimates; see Section 5.3.4.1) Often this requires professional judgment when data are sparse, but the primary objective of this type of estimator is to be within this fairly wide conceptual target range.

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[20]The term "worst case exposure" has historically meant the maximum possible exposure, or where everything that can plausibly happen to maximize exposure, happens. While in actuality, this worst case exposure may fall on the uppermost point of the population distribution, in most cases, it will be somewhat higher than the individual in the population with the highest exposure. The worst case represents a hypothetical individual and an extreme set of conditions; this will usually not be observed in an actual population. The worst case and the so-called maximum exposed individual are therefore not synonymous, the former describing a statistical possibility that may or may not occur in the population, and the latter ostensibly describing an individual that does, or is thought to, exist in the population.

[21]The lower part of the high-end exposure range, e.g., conceptually above the 90th percentile but below about the 98th percentile, has generally been the target used by those employing the term "reasonable worst case exposure." Above about the 98th percentile has been termed the "maximum exposure" range. Note that both these terms should refer to estimates of exposure on the actual distribution, not above it.

The relationship between answering the questions about high-end individual risk and what the exposure assessor must do to develop the descriptors is discussed in Section 3.4. Individual risk descriptors will generally require the assessor to make estimates of high-end exposure or dose, and sometimes additional estimates (e.g., estimates of central tendency such as average or median exposure or dose).

Another type of individual risk descriptor results from specific sets of circumstances that can be hypothesized as part of a scenario, for example:

- What if a homeowner lives at the edge of this site for his entire life?
- What if a pesticide applicator applies this pesticide without using protective equipment?
- What if a consumer uses this product every day for ten years? Once a month? Once a week?
- What risk level will occur if we set the standard at 100 ppb?

The assumptions made in answering these assessment-specific postulated questions should not be confused with the approximations made in developing an exposure estimate for an existing population or with the adjustments in parameter values made in performing a sensitivity analysis. The assumptions in these specific questions address a purer "if/then" relationship and, as such, are more helpful in answering specific hypothetical or anecdotal questions. The answers to these postulated questions do not give information about how likely the combination of values might be in the actual population or about how many (if any) persons might actually be subjected to the calculated risk.

Exposure scenarios employing these types of postulated questions are encountered often in risk assessments, especially in those where actual exposure data are incomplete or nonexistent. Although the estimates of individual exposure derived from these assumptions provide numerical values for calculating risk, they do so more as a matter of context than a determination of actual exposure. They are not the same types of estimates as high-end exposure or risk, where some statement must be made about the likelihood of their falling within a specified range in the actual exposure or risk distribution.

2.3.2. Population Risk

Population risk refers to an estimate of the extent of harm for the population or population segment being addressed. Risk managers may need questions addressed such as the following:

- How many cases of a particular health effect might be probabilistically estimated for a population of interest during a specified time period?

- For noncarcinogens, what portion of the population exceeds the reference dose (RfD), the reference concentration (RfC), or other health concern level?
- For carcinogens, how many persons are above a certain risk level such as 10^{-6} or a series of risk levels such as 10^{-5}, 10^{-4}, etc?
- How do various subgroups fall within the distributions of exposure, dose, and risk?
- What is the risk for a particular population segment?
- Do any particular subgroups experience a high exposure, dose, or risk?

The risk descriptors for population risk can take any of several forms:

- a probabilistic projection of the estimated extent of occurrence of a particular effect for a population or segment (sometimes called "number of cases" of effect);
- a description of what part of the population (or population segment) is above a certain risk value of interest; or
- a description of the distribution of risk among various segments or subgroups of the population.

In theory, an estimate of the extent of effects a population might incur (e.g., the number of individual cases that might occur during a specified time) can be calculated by summing the individual risks for all individuals within the population or population segment of interest. The ability to calculate this estimate depends on whether the individual risks are in terms of probabilities for each individual, rather than a hazard index or other nonprobabilistic risk. The calculation also requires a great deal more information than is normally available.

For some assessments, an alternate method is used, provided certain conditions hold. An arithmetic mean dose is usually much easier to estimate than the individual doses of each person in the population or population segment, but calculating the hypothetical number of cases by using mean doses, slope factors, and population size must be done with considerable caution. If the risk varies linearly with dose, and there is no threshold below which no effect ever occurs, an estimate of the number of cases that might occur can be derived from the definition of arithmetic mean. If $A = T/n$, where A is the arithmetic mean of n numbers, and T is the sum of the same n numbers, simple rearrangement gives $T = A \cdot n$. If the arithmetic mean risk for the population (A) can be estimated, and the size of the population (n) is known, then this relationship can be used to calculate a probabilistic estimate of the extent of effects (T).[22] Even so, several other cautions apply when using this method.

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[22]Since the geometric mean (G) is defined differently, use of the geometric mean individual risk (where G does not equal A, such as is often found in environmental situations) in the above relationship will obviously give an erroneous (usually low) estimate of the total. Geometric means have appropriate uses in exposure and risk assessment, but estimating population risk in this way is not one of them.

Individual risks are usually expressed on an upper bound basis, and the resulting number of cases estimated in this manner will normally be an upper bound estimate due to the nature of the risk model used. This method will not work at all for nonlinear dose-response models, such as many noncancer effects or for nonlinear carcinogenic dose-response models.

In practice, it is difficult even to establish an accurate mean health effect risk for a population. This is due to many complications, including uncertainties in using animal data for human dose-response relationships, nonlinearities in the dose-response curve, projecting incidence data from one group to another dissimilar group, etc. Although it has been common practice to estimate the number of cases of disease, especially cancer, for populations exposed to chemicals, it should be understood that these estimates are not meant to be accurate predictions of real (or actuarial) cases of disease. The estimate's value lies in framing hypothetical risk in an understandable way rather than in any literal interpretation of the term "cases."

Another population risk descriptor is a statement regarding how many people are thought to be above a certain risk level or other point of demarcation. For carcinogens, this might be an excess risk level such as 10^{-6} (or a series of levels, i.e., 10^{-5}, 10^{-4}, etc.). For noncarcinogenic risk, it might be the portion of the population that exceeds the RfD (a dose), the RfC (an exposure concentration), an effect-based level such as a lowest observed adverse effect level (LOAEL), etc. For the exposure assessor, this type of descriptor usually requires detailed information about the distribution of exposures or doses.

Other population risk descriptors address the way the risk burden is distributed among various segments of the subject population. The segments (or subgroups) could be divided by geographic location, age, sex, ethnic background, lifestyle, economic factors, or other demographic variables, or they could represent groups of persons with a typical sensitivity or susceptibility, such as asthmatics.

For assessors, this means that data may need to be evaluated for both highly exposed population segments and highly sensitive population segments. In cases involving a highly exposed population segment, the assessor might approach this question by having this segment of the population in mind when developing the descriptors of high-end exposure or dose. Usually, however, these segments are identified (either *a priori* or from inspection of the data) and then treated as separate, unique populations in themselves, with segment-specific risk descriptors (population, individual, etc.) analogous to those used for the larger population.

2.3.3. Risk Descriptors

In summary, exposure and dose information developed as part of an exposure assessment may be used in constructing risk descriptors. These are statements to convey information about risk to users of that information, primarily risk managers. Risk descriptors can be grouped as

descriptors of individual risk or population risk, and within these broad categories, there are several types of descriptors. Not all descriptors are applicable to all assessments. As a matter of policy, the Agency or individual program offices within the Agency may require one or more of these descriptors to be included in specific risk assessments. Because the type of descriptor translates fairly directly into the type of analysis the exposure assessor must perform, the exposure assessor needs to be aware of these policies. Additional information on calculating and presenting exposure estimates and risk descriptors is found in Sections 5 and 7 of these Guidelines.

3. PLANNING AN EXPOSURE ASSESSMENT

Exposure assessments are done for a variety of purposes, and for that reason, cannot easily be regimented into a set format or protocol. Each assessment, however, uses a similar set of planning questions, and by addressing these questions the assessor will be better able to decide what is needed to perform the assessment and how to obtain and use the information required. To facilitate this planning, the exposure assessor should consider some basic questions:

Purpose: Why is the study being conducted? What questions will the study address and how will the results be used?
Scope: Where does the study area begin and end? Will inferences be made on a national, regional, or local scale? Who or what is to be monitored? What chemicals and what media will be measured, and for which individuals, populations, or population segments will estimates of exposure and dose be developed?
Level of Detail: How accurate must the exposure or dose estimate be to achieve the purpose? How detailed must the assessment be to properly account for the biological link between exposure, dose, effect, and risk, if necessary? How is the depth of the assessment limited by resources (time and money), and what is the most effective use of those resources in terms of level of detail of the various parts of the assessment?
Approach: How will exposure or dose be measured or estimated, and are these methods appropriate given the biological links among exposure, dose, effect, and risk? How will populations be characterized? How will exposure concentrations be estimated? What is known about the environmental and biological fate of the substance? What are the important exposure pathways? What is known about expected concentrations, analytical methods, and detection limits? Are the presently available analytical methods capable of detecting the chemical of interest and can they achieve the level of quality needed in the assessment? How many samples are needed? When will the samples be collected? How frequently? How will the data be handled, analyzed, and interpreted?

By addressing each of these questions, the exposure assessor will develop a clear and concise definition of study objectives that will form the basis for further planning.

3.1. PURPOSE OF THE EXPOSURE ASSESSMENT

The particular purpose for which an exposure assessment will be used will often have significant implications for the scope, level of detail, and approach of the assessment. Because

of the complex nature of exposure assessments, a multidisciplinary approach that encompasses the expertise of a variety of scientists is necessary. Exposure assessors should seek assistance from other scientists when they lack the expertise necessary in certain areas of the assessment.

3.1.1. Using Exposure Assessments in Risk Assessment

The National Research Council (NRC, 1983) described exposure assessment as one of the four major areas of risk assessment (the others are hazard identification, dose-response assessment, and risk characterization). The primary purpose of an exposure assessment in this application is often to estimate dose, which is combined with chemical-specific dose-response data (usually from animal studies) in order to estimate risk. Depending on the purpose of the risk assessment, the exposure assessment will need to emphasize certain areas in addition to quantification of exposure and dose.

If the exposure assessment is part of a risk assessment to support regulations for specific chemical sources, such as point emission sources, consumer products, or pesticides, then the link between the source and the exposed or potentially exposed population is important. In this case, it is often necessary to trace chemicals from the source to the point of exposure by using source and fate models and exposure scenarios. By examining the individual components of a scenario, assessors can focus their efforts on the factors that contribute the most to exposure, and perhaps use the exposure assessment to select possible actions to reduce risk. For example, exposure assessments are often used to compare and select control or cleanup options. Most often the scenario evaluation is employed to estimate the residual risk associated with each of the alternatives under consideration. These estimates are compared to the baseline risk to determine the relative risk reduction of each alternative. These types of assessments can also be employed to make screening decisions about whether to further investigate a particular chemical. These assessments can also benefit from verification through the use of personal or biological monitoring techniques.

If the exposure assessment is part of a risk assessment performed to set standards for environmental media, usually the concentration levels in the medium that pose a particular risk level are important. Normally, these assessments place less emphasis on the ultimate source of the chemical and more emphasis on linking concentration levels in the medium with exposure and dose levels of those exposed. A combination of media measurements and personal exposure monitoring could be very helpful in assessments for this purpose, since what is being sought is the relationship between the two. Modeling may also support or supplement these assessments.

If the exposure assessment is part of a risk assessment used to determine the need to remediate a waste site or chemical spill, the emphasis is on calculating the risk to an individual or small group, comparing that risk to an acceptable risk level, and if necessary determining

appropriate cleanup actions to reach an acceptable risk. The source of chemical contamination may or may not be known. Although personal exposure monitoring can give a good indication of the exposure or dose at the present time, often the risk manager must make a decision that will protect health in the future. For this reason, modeling and scenario development are the primary techniques used in this type of assessment. Emphasis is usually placed on linking sources with the exposed individuals. Biological monitoring may also be helpful (in cases where the methodology is established) in determining if exposure actually results in a dose, since some chemicals are not bioavailable even if intake occurs.

If the exposure assessment is part of a risk assessment used as a screening device for setting priorities, the emphasis is more on the comparative risk levels, perhaps with the risk estimates falling into broad categories (e.g., semi-quantitative categories such as high, medium, and low). For such quick-sorting exercises, rarely are any techniques used other than modeling and scenario development. Decisions made in such cases rarely involve direct cleanup or regulatory action without further refinement of the risk assessment, so the scenario development approach can be a cost-effective way to set general priorities for future investigation of worst risk first.

If the exposure assessment is part of a risk assessment that is wholly predictive in nature, such as for the premanufacture notice (PMN) program, a modeling and scenario development approach is recommended. In such cases, measurement of chemicals yet to be manufactured or in the environment is not possible. In this case again, the link between source and exposed individuals is emphasized.

Not only are risk assessments done for a variety of purposes, but the toxic endpoints being assessed (e.g., cancer, reproductive effects, neurotoxic effects) can also vary widely. Endpoints and other aspects of the hazard identification and dose-response relationships can have a major effect on how the exposure information must be collected and analyzed for a risk assessment. This is discussed in more detail in Section 3.5.1.

3.1.2. Using Exposure Assessments for Status and Trends

Exposure assessments can also be used to determine whether exposure occurs and to monitor status and trends. The emphasis in these exposure assessments is on what the actual exposure (or dose) is at one particular time, and how the exposure changes over time. Examples of this type of assessment are occupational studies. Characteristics and special considerations for occupational studies have been discussed by the National Institute for Occupational Safety and Health (NIOSH, 1988).

Exposure status is the snapshot of exposure at a given time, usually the exposure profile of a population or population segment (perhaps a segment or statistical sample that can be

studied periodically). Exposure trends show how this profile changes with time. Normally, status and trends studies make use of statistical sampling strategies to assure that changes can be interpreted meaningfully. These data are particularly useful if actions for risk amelioration and demonstration of the effectiveness of these actions can be made through exposure trend measurements.

Measurement is critical to such assessments. Personal monitoring can give the most accurate picture of exposure, but biological or media monitoring can indicate exposure levels, provided a strong link is established between the biological or media levels and the exposure levels. Usually this link is established first by correlating biological or media levels with personal monitoring data for the same population over the same period.

3.1.3. Using Exposure Assessments in Epidemiologic Studies

Exposure assessments can also be important components of epidemiologic studies, where the emphasis is on using the exposure assessment to establish exposure-incidence (or dose-effect) relationships. For this purpose, personal monitoring, biological monitoring, and scenario development have all been used. If the population under study is being currently exposed, personal monitoring or biological monitoring may be particularly helpful in establishing exposure or dose levels. If the exposure took place in the past, biological monitoring may provide useful data, provided the chemical is amenable to detection without interference or degradation, and the pharmacokinetics are known. More often, however, scenario development techniques are used to estimate exposure in the past, and often the accuracy of the estimate is limited to classifying exposure as high, medium, or low. This type of categorization is rather common, but sometimes it is very difficult to determine who belongs in a category, and to interpret the results of the study. Although epidemiologic protocols are beyond the scope of these Guidelines, the use of exposure assessment for epidemiology has been described by the World Health Organization (WHO, 1983).

3.2. SCOPE OF THE ASSESSMENT

The scope of an assessment refers to its comprehensiveness. For example, an important limitation in many exposure assessments relates to the specific chemical(s) to be evaluated. Although this seems obvious, where exposure to multiple chemicals or mixtures is possible, it is not always clear whether assessing "all" chemicals will result in a different risk value than if only certain significant chemicals are assessed and the others assumed to contribute only a minor amount to the risk. This may also be true for cases where degradation products have equal or greater toxicological concerns. In these cases, a preliminary investigation may be necessary to determine which chemicals are likely to be in high enough concentrations to cause concern, with

the possible contribution of the others discussed in the uncertainty assessment. The assessor must also determine geographical boundaries, population exposed, environmental media to be considered, and exposure pathways and routes of concern.

The purpose of the exposure assessment will usually help define the scope. There are characteristics that are unique to national exposure assessments as opposed to industry-wide or local exposure assessments. For example, exposure assessments in support of national regulations must be national in scope; exposure assessments to support cleanup decisions at a site will be local in scope. Exposure assessments to support standards for a particular medium will often concentrate on that medium's concentration levels and typical exposure pathways and routes, although the other pathways and routes are also often estimated for perspective.

3.3. LEVEL OF DETAIL OF THE ASSESSMENT

The level of detail, or depth of the assessment, is measured by the amount and resolution of the data used, and the sophistication of the analysis employed. It is determined by the purpose of the exposure assessment and the resources available to perform the assessment. Although in theory the level of detail needed can be established by determining the accuracy of the estimate required, this is rarely the case in practice. To conserve resources, most assessments are done in an iterative fashion, with a screening done first; successive iterations add more detail and sophistication. After each iteration, the question is asked, is this level of detail or degree of confidence good enough to achieve the purpose of the assessment? If the answer is no, successive iterations continue until the answer is affirmative, new input data are generated, or as is the case for many assessments, the available data, time, or resources are depleted. Resource-limited assessments should be evaluated in terms of what part of the original objectives have been accomplished, and how this affects the use of the results.

The level of detail of an exposure assessment can also be influenced by the level of sophistication or uncertainty in the assessment of health effects to be used for a risk assessment. If only very weak health information is available, a detailed, costly, and in-depth exposure assessment will in most cases be wasteful, since the most detailed information will not add significantly to the certainty of the risk assessment.

3.4. DETERMINING THE APPROACH FOR THE EXPOSURE ASSESSMENT

The intended use of the exposure assessment will generally favor one approach to quantifying exposure over the others, or suggest that two or more approaches be combined. These approaches to exposure assessment can be viewed as different ways of estimating the same exposure or dose. Each has its own unique characteristics, strengths, and weaknesses, but the estimate should theoretically be the same, independent of the approach taken.

The point-of-contact approach requires measurements of chemical concentrations at the point where they contact the exposed individuals, and a record of the length of time of contact at each concentration. Some integrative techniques are inexpensive and easy to use (radiation badges), while others are costly and may present logistical challenges (personal continuous-sampling devices), and require public cooperation.

The scenario evaluation approach requires chemical concentration and time-of-contact data, as well as information on the exposed persons. Chemical concentration may be determined by sampling and analysis or by use of fate and transport models (including simple dilution models). Models can be particularly helpful when some analytical data are available, but resources for additional sampling are limited. Information on human behavior and physical characteristics may be assumed or obtained by interviews or other techniques from individuals who represent the population of interest.

For the reconstruction of dose approach, the exposure assessor usually uses measured body burden or specific biomarker data, and selects or constructs a biological model that uses these data to account for the chemical's behavior in the body. If a pharmacokinetic model is used, additional data on metabolic processes will be required (as well as model validation information). Information on exposure routes and relative source strengths is also helpful.

One of the goals in selecting the approach should include developing an estimate having an acceptable amount of uncertainty. In general, estimates based on quality-assured measurement data, gathered to directly answer the questions of the assessment, are likely to have less uncertainty than estimates based on indirect information. The approach selected for the assessment will determine which data are needed. All three approaches also require data on intake and uptake rates if the final product of the assessment is a calculated dose.

Sometimes more than one approach is used to estimate exposure. For example, the TEAM study combines point-of-contact measurement with the microenvironment (scenario evaluation) approach and breath measurements for the reconstruction of dose approach (U.S. EPA, 1987a). If more than one approach is used, the assessor should consider how using each approach separately can verify or validate the others. In particular, point-of-contact measurements can be used as a check on assessments made by scenario evaluation.

3.5. ESTABLISHING THE EXPOSURE ASSESSMENT PLAN

Before starting work on an exposure assessment, the assessor should have determined the purpose, scope, level of detail, and approach for the assessment, and should be able to translate these into a set of objectives. These objectives will be the foundation for the exposure assessment plan. The exposure assessment plan need not be a lengthy or formal document,

especially for assessments that have a narrow scope and little detail. For more complex exposure assessments, however, it is helpful to have a written plan.

For exposure assessments being done as part of a risk assessment, the exposure assessment plan should reflect (in addition to the objectives) an understanding of how the results of the exposure assessment will be used in the risk assessment. For some assessments, three additional components may be needed: the sampling strategy (Section 3.5.2), the modeling strategy (Section 3.5.3), and the communications strategy (Section 7.1.3).

3.5.1. Planning an Exposure Assessment as Part of a Risk Assessment

For risk assessments, exposure information must be clearly linked to the hazard identification and dose-response relationship (or exposure-response relationship; see Section 3.5.4). The toxic endpoints (e.g., cancer, reproductive effects, neurotoxic effects) can vary widely, and along with other aspects of the hazard identification and dose-response relationships, can have a major effect on how the exposure information must be collected and analyzed for a risk assessment. Some of these aspects include implications of limited versus repeated exposures, dose-rate considerations, reversibility of toxicological processes, and composition of the exposed population.

- **Limited Versus Repeated Exposures.** Current carcinogen risk models often use lifetime time-weighted average doses in the dose-response relationships owing to their derivation from lifetime animal studies. This does not mean cancer cannot occur after single exposures (witness the A-bomb experience), merely that exposure information must be consonant with the source of the model. Some toxic effects, however, occur after a single or a limited number of exposures, including acute reactions such as anesthetic effects and respiratory depression or certain developmental effects following exposure during pregnancy. For developmental effects, for example, lifetime time-weighted averages have little relevance, so different types of data must be collected, in this case usually shorter-term exposure profile data during a particular time window. Consequently, the exposure assessors and scientists who conduct monitoring studies need to collaborate with those scientists who evaluate a chemical's hazard potential to assure the development of a meaningful risk assessment. If short-term peak exposures are related to the effect, then instruments used should be able to measure short-term peak concentrations. If cumulative exposure is related to the effect, long-term average sampling strategies will probably be more appropriate.
- **Dose-Rate Effects.** The use of average daily exposure values (e.g., ADD, LADD) in a dose-response relationship assumes that within some limits, increments of C times T (exposure concentration times time) that are equal in magnitude are equivalent in their

potential to cause an effect, regardless of the pattern of exposure (the so-called Haber's Rule; see Atherley, 1985). In those cases where toxicity depends on the dose rate, one may need a more precise determination of the time people are exposed to various concentrations and the sequence in which these exposures occur.

- **Reversibility of Toxicological Processes.** The averaging process for daily exposure assumes that repeated dosing continues to add to the risk potential. In some cases, after cessation of exposure, toxicological processes are reversible over time. In these cases, exposure assessments must provide enough information so that the risk assessor can account for the potential influence of episodic exposures.
- **Composition of the Exposed Population.** For some substances, the type of health effect may vary as a function of age or sex. Likewise, certain behaviors (e.g., smoking), diseases (e.g., asthma), and genetic traits (e.g., glucose-6-phosphate dehydrogenase deficiency) may affect the response of a person to a chemical substance. Special population segments, such as children, may also call for a specialized approach to data collection (WHO, 1986).

3.5.2. Establishing the Sampling Strategy

If the objectives of the assessment are to be met using measurements, it is important to establish the sampling strategy before samples are actually taken. The sampling strategy includes setting data quality objectives, developing the sampling plan and design, using spiked and blank samples, assessing background levels, developing quality assurance project plans, validating previously generated data, and selecting and validating analytical methods.

3.5.2.1. *Data Quality Objectives*

All measurements are subject to uncertainty because of the inherent variability in the quantities being measured (e.g., spatial and temporal variability) and analytical measurement variability introduced during the measurement process through sampling and analysis. Some sources of variability can be expressed quantitatively, but others can only be described qualitatively. The larger the variability associated with individual measurements, the lower the data quality, and the greater the probability of errors in interpretation. Data quality objectives (DQOs) describe the degree of uncertainty that an exposure assessor and other scientists and management are willing to accept.

Realistic DQOs are essential. Data of insufficient quality will have little value for problem solving, while data of quality vastly in excess of what is needed to answer the questions asked provide few, if any, additional advantages. DQOs should consider data needs, cost-effectiveness, and the capability of the measurement process. The amount of data required

depends on the level of detail necessary for the purpose of the assessment. Estimates of the number of samples to be taken and measurements to be made should account for expected sample variability. Finally, DQOs help clarify study objectives by compelling the exposure assessor to establish how the data will be used before they are collected.

The exposure assessor establishes data criteria by proposing limits (based on best judgment or perhaps a pilot study) on the acceptable level of uncertainty for each conclusion to be drawn from new data, considering the resources available for the study. DQOs should include:

- A clear statement of study objectives, to include an estimation of the key study parameters, identifying the hypotheses being tested, the specific aims of the study, and how the results will be used.
- The scope of study objectives, to include the minimum size of subsamples from which separate results may be calculated, and the largest unit (area, time period, or group of people) the data will represent.
- A description of the data to be obtained, the media to be sampled, and the capabilities of the analytical methodologies.
- The acceptable probabilities and uncertainties associated with false positive and false negative statements.
- A discussion of statistics used to summarize the data; any standards, reference values, or action levels used for comparison; and a description and rationale for any mathematical or statistical procedures used.
- An estimate of the resources needed.

3.5.2.2. *Sampling Plan*

The sampling plan specifies how a sample is to be selected and handled. An inadequate plan will often lead to biased, unreliable, or meaningless results. Good planning, on the other hand, makes optimal use of limited resources and is more likely to produce valid results.

The sampling design specifies the number and types of samples needed to achieve DQOs. Factors to be considered in developing the sampling design include study objectives, sources of variability (e.g., temporal and spatial heterogeneity, analytical differences) and their relative magnitudes, relative costs, and practical limitations of time, cost, and personnel.

Sampling design considers the need for temporal and spatial replication, compositing (combining several samples prior to analysis), and multiple determinations on a single sample. A statistical or environmental process model may be used to allocate sampling effort in the most efficient manner.

Data may be collected using a survey or an experimental approach. It may be desirable to stratify the sample if it is suspected that differences exist between segments of the statistical population being sampled. In such cases, the stratified sampling plan assures representative samples of the obviously different parts of the sample population while reducing variance in the sample data. The survey approach estimates population exposure based on the measured exposure of a statistically representative sample of the population. In some situations the study objectives are better served by an experimental approach; this approach involves experiments designed to determine the relationship between two or more factors, (e.g., between house construction and a particular indoor air pollutant). In the experimental approach, experimental units are selected to cover a range of situations (e.g., different housing types), but do not reflect the frequency of those units in the population of interest. An understanding of the relationship between factors gained from an experiment can be combined with other data (e.g., distribution of housing types) to estimate exposure. An advantage of the experimental approach is that it may provide more insight into underlying mechanisms which may be important in targeting regulatory action. However, as in all experimental work, one must argue that the relationships revealed apply beyond that particular experiment.

A study may use a combination of survey and experimental techniques and involve a variety of sampling procedures. A summary of methods for measuring worker exposure is found in Lynch (1985). Smith et al. (1987) provide guidance for field sampling of pesticides. Relevant EPA reference documents include Survey Management Handbook, Volumes I and II (U.S. EPA, 1984b); Soil Sampling Quality Assurance User's Guide (U.S. EPA, 1990a); and A Rationale for the Assessment of Errors in the Sampling of Soils (U.S. EPA, 1989a). A detailed description of methods for enumerating and characterizing populations exposed to chemical substances is contained in Methods for Assessing Exposure to Chemical Substances, Volume 4 (U.S. EPA, 1985a).

Factors to be considered in selecting sampling locations include population density, historical sampling results, patterns of environmental contamination and environmental characteristics such as stream flow or prevailing wind direction, access to the sample site, types of samples, and health and safety requirements.

The frequency and duration of sample collection will depend on whether the risk assessor is concerned with acute or chronic exposures, how rapidly contamination patterns are changing, ways in which chemicals are released into the environment, and whether and to what degree physical conditions are expected to vary in the future.

There are many sources of information on methods for selecting sampling locations. Schweitzer and Black (1985) and Schweitzer and Santolucito (1984) give statistical methods for selecting sampling locations for ground water, soil, and hazardous wastes. A practical guide for

ground-water sampling (U.S. EPA, 1985b) and a handbook for stream sampling (U.S. EPA, 1986d) are also available.

The type of sample to be taken and the physical and chemical properties of the chemical of concern usually dictate the sampling frequency. For example, determining the concentration of a volatile chemical in surface water requires a higher sampling frequency than necessary for ground water because the chemical concentration of the surface water changes more rapidly. Sampling frequency might also depend on whether the health effects of concern result from acute or chronic exposures. More frequent sampling may be needed to determine peak exposures versus average exposure.

A preliminary survey is often used to estimate the optimum number, spacing, and sampling frequency. Factors to be considered include technical objectives, resources, program schedule, types of analyses, and the constituents to be evaluated. Shaw et al. (1984), Sanders and Adrian (1978), and Nelson and Ward (1981) discuss statistical techniques for determining the optimal number of samples.

Sampling duration depends on the analytical method chosen, the limits of detection, the physical and chemical properties of the analyte, chemical concentration, and knowledge of transport and transformation mechanisms. Sampling duration may be extended to ensure adequate collection of a chemical at low concentration or curtailed to prevent the breakthrough of one at high concentration. Sampling duration is directly related to selection of statistical procedures, such as trend or cross-sectional analyses.

Storage stability studies with periodic sample analysis should normally be run concurrently with the storage of treated samples. However, in certain situations where chemicals are prone to break down or have high volatility, it is advisable to run a storage stability study in advance so that proper storage and maximum time of storage can be determined prior to sample collection and storage. Unless storage stability has been previously documented, samples should be analyzed as soon as possible after collection to avoid storage stability problems. Individual programs may have specific time limits on storage, depending on the types of samples being analyzed.

3.5.2.3. *Quality Assurance Samples*

Sampling should be planned to ensure that the samples are not biased by the introduction of field or laboratory contaminants. If sample validity is in question, all associated analytical data will be suspect. Field- and laboratory-spiked samples and blank samples should be analyzed concurrently to validate results. The plan should provide instructions clear enough so that each worker can collect, prepare, preserve, and analyze samples according to established protocols.

Any data not significantly greater than blank sample levels should be used with considerable caution. All values should be reported as measured by the laboratory, but with appropriate caveats on blank sample levels. The method for interpreting and using the results from blank samples depends on the analyte and should be specified in the sampling plan. The following guidance is recommended:

- For volatiles and semivolatiles, no positive sample results should be reported unless the concentration of the compound in the sample exceeds 10 times the amount in any blank for the common laboratory contaminants methylene chloride, acetone, toluene, 2-butanone, and common phthalate esters. The amount for other volatiles and semivolatiles should exceed 5 times the amount in the blank (U.S. EPA, 1988d).
- For pesticides and polychlorinated biphenyls (PCBs) no positive sample results should be reported unless the concentration in the sample exceeds 5 times that in the blank (U.S. EPA, 1988d). If a pesticide or PCB is found in a blank but not in a sample, no action is taken.
- For inorganics, no positive sample results should be reported if the results are less than 5 times the amount in any blank (U.S. EPA, 1988e).

3.5.2.4. *Background Level*

Background presence may be due to natural or anthropogenic sources. At some sites, it is significant and must be accounted for. The exposure assessor should try to determine local background concentrations by gathering data from nearby locations clearly unaffected by the site under investigation.

When differences between a background (control area) and a target site are to be determined experimentally, the control area must be sampled with the same detail and care as the target.

3.5.2.5. *Quality Assurance and Quality Control*

Quality assurance (QA) assures that a product meets defined standards of quality with a stated level of confidence. QA includes quality control.

Quality assurance begins with the establishment of DQOs and continues throughout the measurement process. Each laboratory should have a QA program and, for each study, a detailed quality assurance project plan, with language clear enough to preclude confusion and misunderstanding. The plan should list the DQOs and fully describe the analytes, all materials, methods, and procedures used, and the responsibilities of project participants. The EPA has prepared a guidance document (U.S. EPA, 1980) that describes all these elements and provides complete guidance for plan preparation. Quality control (QC) ensures a product or service is

satisfactory, dependable, and economical. A QC program should include development and strict adherence to principles of good laboratory practice, consistent use of standard operational procedures, and carefully-designed protocols for each measurement effort. The program should ensure that errors have been statistically characterized and reduced to acceptable levels.

3.5.2.6. *Quality Assurance and Quality Control for Previously Generated Data*

Previously generated data may be used by the exposure assessor to fulfill current needs. Any data developed through previous studies should be validated with respect to both quality and extrapolation to current use. One should consider how long ago the data were collected and whether they are still representative. The criteria for method selection and validation should also be followed when analyzing existing data. Other points considered in data evaluation include the collection protocol, analytical methods, detection limits, laboratory performance, and sample handling.

3.5.2.7. *Selection and Validation of Analytical Methods*

There are several major steps in the method selection and validation process. First, the assessor establishes methods requirements. Next, existing methods are reviewed for suitability to the current application. If a new method must be developed, it is subjected to field and laboratory testing to determine its performance; these tests are then repeated by other laboratories using a round robin test. Finally, the method is revised as indicated by laboratory testing. The reader is referred to Guidance for Data Useability in Risk Assessment (U.S. EPA, 1990b) for extensive discussion of this topic.

3.5.3. Establishing the Modeling Strategy

Often the most critical element of the assessment is the estimation of pollutant concentrations at exposure points. This is usually carried out by a combination of field data and mathematical modeling results. In the absence of field data, this process often relies on the results of mathematical models (U.S. EPA, 1986e, 1987b, 1987c, 1988f, 1991b). EPA's Science Advisory Board (U.S. EPA, 1989b) has concluded that, ideally, modeling should be linked with monitoring data in regulatory assessments, although this is not always possible (e.g., for new chemicals).

A modeling strategy has several aspects, including setting objectives, model selection, obtaining and installing the code, calibrating and running the computer model, and validation and verification. Many of these aspects are analogous to the QA/QC measures applied to measurements.

3.5.3.1. *Setting the Modeling Study Objectives*

The first step in using a model to estimate concentrations and exposure is to clearly define the goal of the exposure assessment and how the model can help address the questions or hypotheses of the assessment. This includes a clear statement of what information the model will help estimate, and how this estimate will be used. The approach must be consistent with known project constraints (i.e., schedule, budget, and other resources).

3.5.3.2. *Characterization and Model Selection*

Regardless of whether models are extensively used in an assessment and a formal modeling strategy is documented in the exposure assessment plan, when computer simulation models such as fate and transport models and exposure models are used in exposure assessments, the assessor must be aware of the performance characteristics of the model and state how the exposure assessment requirements are satisfied by the model.

If models are to be used to simulate pollutant behavior at a specific site, the site must be characterized. Site characterization for any modeling study includes examining all data on the site such as source characterization, dimensions and topography of the site, location of receptor populations, meteorology, soils, geohydrology, and ranges and distributions of chemical concentrations. For exposure models that simulate both chemical concentration and time of exposure (through behavior patterns) data on these two parameters must be evaluated.

For all models, the modeler must determine if databases are available to support the site, chemical, or population characterization, and that all parameters required by the model can be obtained or reasonable default values are available. The assessment goals and the results of the characterization step provide the technical basis for model selection.

Criteria are provided in U.S. EPA (1987b, 1988f) for selection of surface water models and ground-water models respectively; the reader is referred to these documents for details. Similar selection criteria exist for air dispersion models (U.S. EPA, 1986e, 1987c, 1991b).

A primary consideration in selecting a model is whether to perform a screening study or to perform a detailed study. A screening study makes a preliminary evaluation of a site or a general comparison between several sites. It may be generic to a type of site (i.e., an industrial segment or a climatic region) or may pertain to a specific site for which sufficient data are not available to properly characterize the site. Screening studies can help direct data collection at the site by, for example, providing an indication of the level of detection and quantification that would be required and the distances and directions from a point of release where chemical concentrations might be expected to be highest.

The value of the screening-level analysis is that it is simple to perform and may indicate that no significant contamination problem exists. Screening-level models are frequently used to

get a first approximation of the concentrations that may be present. Often these models use very conservative assumptions; that is, they tend to overpredict concentrations or exposures. If the results of a conservative screening procedure indicate that predicted concentrations or exposures are less than some predetermined no-concern level, then a more detailed analysis is probably not necessary. If the screening estimates are above that level, refinement of the assumptions or a more sophisticated model are necessary for a more realistic estimate.

Screening-level models also help the user conceptualize the physical system, identify important processes, and locate available data. The assumptions used in the preliminary analysis should represent conservative conditions, such that the predicted results overestimate potential conditions, limiting false negatives. If the limited field measurements or screening analyses indicate that a contamination problem may exist, then a detailed modeling study may be useful.

A detailed study is one in which the purpose is to make a detailed evaluation of a specific site. The approach is to use the best data available to make the best estimate of spatial and temporal distributions of chemicals. Detailed studies typically require much more data of higher quality and models of greater sophistication.

3.5.3.3. *Obtaining and Installing the Computer Code*

It may be necessary to obtain and install the computer code for a model on a specific computer system. Modern computer systems and software have a variety of differences that require changes to the source code being installed. It is essential to verify that these modifications do not change the way the model works or the results it provides. If the model is already installed and supported on a computer system to which the user has access, this step is simplified greatly.

Criteria for using a model include its demonstrated acceptability and the ease with which the model can be obtained. Factors include availability of specific models and their documentation, verification, and validation. These so-called implementation criteria relate to the practical considerations of model use and may be used to further narrow the selection of technically acceptable models.

3.5.3.4. *Calibrating and Running the Model*

Calibration is the process of adjusting selected model parameters within an expected range until the differences between model predictions and field observations are within selected criteria. Calibration is highly recommended for all operational, deterministic models. Calibration accounts for spatial variations not represented by the model formulation; functional dependencies of parameters that are either nonquantifiable, unknown, or not included in the model algorithms; or extrapolation of laboratory measurements to field conditions.

Extrapolation of laboratory measurements to field conditions requires considerable care since many unknown factors may cause differences between laboratory and field.

The final step in the modeling portion of an exposure assessment is to run the model and generate the data needed to answer the questions posed in the study objectives.

Experience and familiarity with a model can also be important. This is especially true with regard to the more complex models. Detailed models can be quite complex with a large number of input variables, outputs, and computer-related requirements. It frequently takes months to years of experience to fully comprehend all aspects of a model. Consequently, it is suggested that an exposure assessor select a familiar model if it possesses all the selection criteria, or seek the help of experienced exposure modelers.

3.5.3.5. *Model Validation*

Model validation is a process by which the accuracy of model results is compared with actual data from the system being simulated. There are numerous levels of validation of an environmental fate model, for example, such as verifying that the transport and transformation concepts are appropriately represented in the mathematical equations, verifying that the computer code is free from error, testing the model against laboratory microcosms, running field tests under controlled conditions, running general field tests, and repeatedly comparing field data to the modeling results under a variety of conditions and chemicals. In essence, validation is an independent test of how well the model (with its calibrated parameters) represents the important processes occurring in the natural system. Although field and environmental conditions are often different during the validation step, parameters fixed as a result of calibration are not readjusted during validation.[23]

The performance of models (their ability to represent measured data) is often dramatically influenced by site characterization and how models represent such characteristics. Characterizing complex, heterogenous physical systems presents major challenges; modeling representations of such systems must be evaluated in light of that difficulty. In many cases, the apparent inability to model a system is caused by incomplete physical characterization of the system. In other cases the uncertainties cannot be readily apportioned between the model per se and the model's input data.

In addition to comparing model results with actual data (thus illustrating accuracy, bias, etc.), the model validation process provides information about conditions under which a simulation will be acceptable and accurate, and under what conditions it should not be used at

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[23]In other words, a fundamental rule is that a model should not be validated using data that were already used to generate or calibrate the model, since doing so would not be an independent test.

all. All models have specific ranges of application and specific classes of chemicals for which they are appropriate. Assessors should be aware of these limitations as they develop modeling strategies.

3.5.4. Planning an Exposure Assessment to Assess Past Exposures

In addition to the considerations discussed in Sections 3.5.1 through 3.5.3, if the data are being collected to assess past exposures, such as in epidemiologic studies, they need to be representative of the past exposure conditions, which may have changed with time. The scope and level of detail of the assessment depends greatly on the availability and quality of past data. Several approaches for determining and estimating past exposure are provided in the literature (Waxweiler et al., 1988; Stern et al., 1986; NIOSH, 1988; Greife et al., 1988; Hornung and Meinhardt, 1987).

4. GATHERING AND DEVELOPING DATA FOR EXPOSURE ASSESSMENTS

The information needed to perform an exposure assessment will depend on the approach(es) selected in the planning stage (Section 3). For those assessments using point-of-contact measurements, the information includes:

- Measured exposure concentrations and duration of contact.

For assessments using the scenario evaluation method for estimating exposures, the needed information includes:

- Information on chemical concentrations in media, usually desirable in the format of a concentration-time-location profile.
- Information on persons who are exposed and the duration of contact with various concentrations.

For assessments estimating exposure from dose, the information includes:

- Biomarker data.
- Pharmacokinetic relationships, including the data to support pharmacokinetic models.

If dose is to be calculated, data are needed on:

- Intake and uptake, usually in the form of rates.

Information on sources, both natural and anthropogenic is usually helpful. If the agent has natural sources, the contribution of these to environmental concentrations may be relevant. These background concentrations may be particularly important when the results of toxicity tests show a threshold or distinctly nonlinear dose-response relationship. In a situation where only relative or additional risk is considered, background levels may not be relevant.

4.1. MEASUREMENT DATA FOR POINT-OF-CONTACT ASSESSMENTS

This approach requires that chemical concentrations be measured at the interface between the person and the environment, usually through the use of personal monitors; there are currently no models to assist in the process of obtaining the concentration-time data itself. The chemical concentrations contacted in the media are measured by sampling the individual's breathing zone, food, and water. These methodologies were originally developed for occupational monitoring; they may have to be modified for exposures outside the workplace. An example of this is the development of a small pump and collector used in the TEAM studies (U.S. EPA, 1987a). In order to conduct these studies, a monitoring device had to be developed that was sufficiently small and lightweight so that it could be worn by the subjects.

The Total Human Exposure and Indoor Air Quality (U.S. EPA, 1988h) report is a useful bibliography covering models, field data, and emerging research methodologies, as well as new techniques for accurately determining exposure at nonoccupational levels.

New data for a particular exposure assessment may be developed through the use of point-of-contact methods, or data from prior studies can sometimes be used. In determining whether existing point-of-contact monitoring data can be used in another assessment, the assessor must consider the factors that existed in the original study and that influenced the exposure levels measured. Some of these factors are proximity to sources, activities of the studied individuals, time of day, season, and weather conditions.

Point-of-contact data are valuable in evaluating overall population exposure and checking the credibility of exposure estimates generated by other methods.

4.2. OBTAINING CHEMICAL CONCENTRATION INFORMATION

The distribution of chemical concentrations is used to estimate the concentration that comes in contact with the individual(s) at any given time and place. This can be done through personal monitoring, but for a variety of reasons, in a given assessment, personal monitoring may not be feasible. Alternative methods involve measuring the concentration in the media, or modeling the concentration distribution based on source strength, media transport, and chemical transformation processes. For exposure scenario evaluation, measurements and modeling of media concentrations are often used together.

Many types of measurements can be used to help determine the distribution of chemical concentrations in media. They can be measurements of the concentrations in the media themselves, measurements of source strength, or measurements of environmental fate processes which will allow the assessor to use a model to estimate the concentration in the media at the point of contact. Table 2 illustrates some of the types of measurements used by exposure assessors, along with notes concerning what additional information is usually needed to use these measurements in estimating exposure or dose. For epidemiologic studies, questionnaires are often used when data are not measurable or are otherwise unavailable.

4.2.1. Concentration Measurements in Environmental Media

Measured concentration data can be generated for the exposure assessment by a new field study, or by evaluating concentration data from completed field study results and using them to estimate concentrations. Media measurements taken close to the point of contact with the individual(s) in space and time are preferable to measurements far removed geographically or temporally. As the distance from the point of contact increases, the certainty of the data at the

Table 2. Examples of types of measurements to characterize exposure-related media and parameters[a]

Type of measurement (sample)	Usually attempts to characterize (whole)	Examples	Typical information needed to characterize exposure
A. FOR USE IN EXPOSURE SCENARIO EVALUATION			
1. Fixed-location monitoring	Environmental medium; samples used to establish long-term indications of media quality and trends.	National Stream Quality Accounting Network (NASQAN),[b] water quality networks, air quality networks.	Population location and activities relative to monitoring locations; fate of pollutants over distance between monitoring and point of exposure; time variation of pollutant concentration at point of exposure.
2. Short-term media monitoring	Environmental or ambient medium; samples used to establish a snapshot of quality of medium over relatively short time.	Special studies of environmental media, indoor air.	Population location and activities (this is critical since it must be closely matched to variations in concentrations due to short period of study); fate of pollutants between measurement point and point of exposure; time variation of pollutant concentration at point of exposure.
3. Source monitoring of facilities	Release rates to the environment from sources (facilities). Often given in terms of relationships between release amounts and various operating parameters of the facilities.	Stack sampling, effluent sampling, leachate sampling from landfills, incinerator ash sampling, fugitive emissions sampling, pollution control device sampling.	Fate of pollutants from point of entry into the environment to point of exposure; population location and activities; time variation of release.
4. Food samples (also see #9 below)	Concentrations of contaminants in food supply.	FDA Total Diet Study Program,[c] market basket studies, shelf studies, cooked-food diet sampling.	Dietary habits of various age, sex, or cultural groups. Relationship between food items sampled and groups (geographic, ethnic, demographic) studied. Relationships between concentrations in uncooked versus prepared food.
5. Drinking water samples	Concentrations of pollutants in drinking water supply.	Ground Water Supply Survey,[d] Community Water Supply Survey,[e] tap water.	Fate and distribution of pollutants from point of sample to point of consumption. Population served by specific facilities and consumption rates. For exposure due to other uses (e.g., cooking and showering), need to know activity patterns and volatilization rates.

[a]To characterize dose, intake or uptake information is also needed (see Section 2).
[b]U.S. EPA (1985c).
[c]U.S. EPA (1986f).
[d]U.S. EPA (1985c).
[e]U.S. EPA (1985a).

Table 2. Examples of types of measurements to characterize exposure-related media and parameters (continued)

Type of measurement (sample)	Usually attempts to characterize (whole)	Examples	Typical information needed to characterize exposure
6. Consumer Products	Concentration levels of various products.	Shelf surveys, e.g., solvent concentration in household cleaners.[f]	Establish use patterns and/or market share of particular products, individual exposure at various usage levels, extent of passive exposure.
7. Breathing Zone Measurements	Exposure to airborne chemicals.	Industrial hygiene studies, occupational surveys, indoor air studies.	Location, activities, and time spent relative to monitoring locations. Protective measures/avoidance.
8. Microenvironmental Studies	Ambient medium in a defined area, e.g., kitchen, automobile interior, office setting, parking lot.	Special studies of indoor air, house dust, contaminated surfaces, radon measurements, office building studies.	Activities of study populations relative to monitoring locations and time exposed.
9. Surface Soil Sample	Degree of contamination of soil available for contact.	Soil samples at contaminated sites.	Fate of pollution on/in soil; activities of potentially exposed populations.
10. Soil Core	Soil including pollution available for ground-water contamination; can be an indication of quality and trends over time.	Soil sampling at hazardous waste sites.	Fate of substance in soil; speciation and bioavailability, contact and ingestion rates as a function of activity patterns and age.
11. Fish Tissue	Extent of contamination of edible fish tissue.	National Shellfish Survey.[g]	Relationship of samples to food supply for individuals or population of interest; consumption habits; preparation habits.

[f]U.S. EPA (1985a).
[g]U.S. EPA (1986f).

Table 2. Examples of types of measurements to characterize exposure-related media and parameters (continued)

Type of measurement (sample)	Usually attempts to characterize (whole)	Examples	Typical information needed to characterize exposure
B. FOR USE IN POINT-OF-CONTACT MEASUREMENT			
1. Air Pump/Particulates and Vapors	Exposure of an individual or population via the air medium.	TEAM study,[h] carbon monoxide study.[i] Breathing zone sampling in industrial settings.	Direct measurement of individual exposure during time sampled. In order to characterize exposure to population, relationships between individuals and the population must be established as well as relationships between times sampled and other times for the same individuals, and relationships between sampled individuals and other populations. In order to make these links, activities of the sampled individuals compared to populations characterized are needed in some detail.
2. Passive Vapor Sampling	Same as above.	Same as above.	Same as above.
3. Split Sample Food/Split Sample Drinking Water	Exposures of an individual or population via ingestion.	TEAM study.[j]	Same as above.
4. Skin Patch Samples	Dermal exposure of an individual or population.	Pesticide Applicator Survey.[k]	1) Same as above. 2) Skin penetration.
C. FOR USE IN EXPOSURE ESTIMATION FROM RECONSTRUCTED DOSE			
1. Breath	Total internal dose for individuals or population (usually indicative of relatively recent exposures).	Measurement of volatile organic chemicals (VOCs), alcohol. (Usually limited to volatile compounds).	1) Relationship between individuals and population; exposure history (i.e., steady-state or not) pharmacokinetics (chemical half-life), possible storage reservoirs within the body. 2) Relationship between breath content and body burden.

[h]U.S. EPA (1987a).
[i]U.S. EPA (1987a).
[j]U.S. EPA (1987a).
[k]U.S. EPA (1987d).

Table 2. Examples of types of measurements to characterize exposure-related media and parameters (continued)

Type of measurement (sample)	Usually attempts to characterize (whole)	Examples	Typical information needed to characterize exposure
2. Blood	Total internal dose for individuals or population (may be indicative of either relatively recent exposures to fat-soluble organics or long term body burden for metals).	Lead studies, pesticides, heavy metals (usually best for soluble compounds, although blood lipid analysis may reveal lipophilic compounds).	1) Same as above. 2) Relationship between blood content and body burden.
3. Adipose	Total internal dose for individuals or population (usually indicative of long-term averages for fat- soluble organics).	NHATS,[l] dioxin studies, PCBs (usually limited to lipophilic compounds).	1) Same as above. 2) Relationship between adipose content and body burden.
4. Nails, Hair	Total internal dose for individuals or population (usually indicative of past exposure in weeks to months range; can sometimes be used to evaluate exposure patterns).	Heavy metal studies (usually limited to metals).	1) Same as above. 2) Relationship between nails, hair content and body burden.
5. Urine	Total internal dose for individuals or population (usually indicative of elimination rates); time from exposure to appearance in urine may vary, depending on chemical	Studies of tetrachloroethylene[m] and trichloroethylene.[n]	1) Same as above. 2) Relationship between urine content and body burden

[l]U.S. EPA (1986g).
[m]U.S. EPA (1986h).
[n]U.S. EPA (1987e).

point of contact usually decreases, and the obligation for the assessor to show relevance of the data to the assessment at hand becomes greater. For example, an outdoor air measurement, no matter how close it is taken to the point of contact, cannot by itself adequately characterize indoor exposure.

Concentrations can vary considerably from place to place, seasonally, and over time due to changing emission and use patterns. This needs to be considered not only when designing studies to collect new data, but especially when evaluating the applicability of existing measurements as estimates of exposure concentrations in a new assessment. It is a particular concern when the measurement data will be used to extrapolate to long time periods such as a lifetime. Transport and dispersion models are frequently used to help answer these questions.

The exposure assessor is likely to encounter several different types of measurements. One type of measurement used for general indications and trends of concentrations is outdoor fixed-location monitoring. This measurement is used by EPA and other groups to provide a record of pollutant concentration at one place over time. Nationwide air and water monitoring programs have been established so that baseline values in these environmental media can be documented. Although it is not practical to set up a national monitoring network to gather data for a particular exposure assessment, the data from existing networks can be evaluated for relevance to an exposure assessment. These data are usually somewhat removed, and often far removed, from the point of contact. Adapting data from previous studies usually presents challenges similar to those encountered when using network data. If new data are needed for the assessment, studies measuring specific chemicals at specific locations and times can be conducted.

Contaminant concentrations in indoor air can vary as much or more than those in outdoor air. Consequently, indoor exposure is best represented by measurements taken at the point of contact. However, because pollutants such as carbon monoxide can exhibit substantial indoor penetration, indoor exposure estimates should consider potential outdoor as well as indoor sources of the contaminant(s) under evaluation.

Food and drinking water measurements can also be made. General characterization of these media, such as market basket studies (where representative diets are characterized), shelf studies (where foodstuffs are taken from store shelves and analyzed), or drinking water quality surveys, are usually far removed from the point of contact for an individual, but may be useful in evaluating exposure concentrations over a large population. Closer to the point of contact would be measurements of tap water or foodstuffs in a home, and how they are used. In evaluating the relevance of data from previous studies, variations in the distribution systems must be considered as well as the space-time proximity.

Consumer or industrial product analysis is sometimes done to characterize the concentrations of chemicals in products. The formulation of products can change substantially over time, similar products do not necessarily have similar formulations, and regional differences in product formulation can also occur. These should be considered when determining relevance of extant data and when setting up sampling plans to gather new data.

Another type of concentration measurement is the microenvironmental measurement. Rather than using measurements to characterize the entire medium, this approach defines specific zones in which the concentration in the medium of interest is thought to be relatively homogenous, then characterizes the concentration in that zone. Typical microenvironments include the home or parts of the home, office, automobile, or other indoor settings. Microenvironments can also be divided into time segments (e.g., kitchen-day, kitchen-night). This approach can produce measurements that are closely linked with the point of contact both in location and time, especially when new data are generated for a particular exposure assessment. The more specific the microenvironment, however, the greater the burden on the exposure assessor to establish that the measurements are representative of the population of interest. Adapting existing data bases in this area to a particular exposure assessment requires the usual evaluation discussed throughout this section.

The concentration measurement that provides the closest link to the actual point of contact uses personal monitoring, which is discussed in Section 4.3.

4.2.2. Use of Models for Concentration Estimation

If concentrations in the media cannot be measured, they can frequently be estimated indirectly by using related measurements and models. To accomplish this, source and fate information are usually needed. Source characterization data are used as input to transport and transformation models (environmental fate models). These models use a combination of general relationships and situation-specific information to estimate concentrations. In exposure assessments, mathematical models are used extensively to calculate environmental fate and transport, concentrations of chemicals in different environmental media, the distribution of concentrations over space and time, indoor air levels of chemicals, concentrations in foods, etc. In determining the relevance of this type of model for estimating concentrations, the same rules apply as for the measurements of concentrations discussed in the previous section. When concentrations in the media are available, models can be used to interpolate concentrations between measurements. Because models rely on indirect measurements and data remote from the point of contact, statistically valid analytical measurements take precedence when discrepancies arise. When it is necessary to estimate contributions of individual sources to overall concentrations, models are commonly used.

Source characterization measurements usually determine the rate of release of chemicals into the environment from a point of emission such as an incinerator, landfill, industrial facility, or other source. Often these measurements are used to estimate emission factors, or a relationship between releases and facility operations. Since emission factors are usually averages over time, the assessor must determine whether given emission factors from previous work are relevant to the time specificity and source type needed for the exposure assessment. Generally, emission factors are more useful for long-term average emission calculations, and become less useful when applied to intermittent or short-term exposures.

Environmental fate measurements can be either field measurements (field degradation studies, for example) or laboratory measurements (partition coefficients, hydrolysis, or biodegradation rates, etc.). Approximations for these rates can sometimes also be calculated (Lyman et al., 1982).

Environmental fate models calculate estimated concentrations in media, that in turn are linked to the concentrations at the point of contact. The use of estimated properties or rates adds to the uncertainty in the exposure concentration estimate. When assessors use these methods to estimate exposures, uncertainties attributable to the model and the validation status of the model must be clearly discussed in the uncertainty section (see discussion in Section 6).

4.2.3. Selection of Models for Environmental Concentrations

Selection of an appropriate model is essential for successful simulation of chemical concentrations. In most cases assessors will be able to choose between several models, any of which could be used to estimate environmental concentrations. There is no right model; there may not even be a best model. There are, however, several factors that will help in selecting an appropriate model for the study. The assessor should consider the objectives of the study, the technical capabilities of the models, how readily the models can be obtained, and how difficult each is to use (U.S. EPA, 1987b, 1988f).

The primary consideration in selecting a model is the objective of the exposure assessment. The associated schedule, budget, and other resource constraints will also affect model selection options. Models are available to support both screening-level and detailed, site-specific studies. Screening models can provide quick, easy, and cost-effective estimates of environmental concentrations. They can support data collection efforts at the site by indicating the required level of detection and quantification and the locations where chemical concentrations are expected to be highest. They are also used to interpolate chemical concentrations between measurements. Where study objectives require the best estimates of spatial and temporal distributions of chemicals, more sophisticated models are available. These

models require more and better data to characterize the site, and therefore site-specific data may be needed in order to use them.

The technical capabilities of a model are expressed in its ability to simulate site-specific contaminant transport and transformation processes. The model must be able to simulate the relevant processes occurring within the specified environmental setting. It must adequately represent the physical setting (e.g., the geometric configuration of hydrogeological systems, river widths and depths, soil profiles, meteorological patterns, etc.) and the chemical transformation processes. Field data from the area where doses are to be estimated are necessary to define the input parameters required to use the models. In cases in which these data are not available, parameter values representative of field conditions should be used as defaults. Assumptions of homogeneity and simplification of site geometry may allow use of simpler models.

In addition, it is important to thoroughly understand the performance characteristics of the model used. This is especially true with regard to the more complex models. Detailed models can be quite complex with a large number of input variables, outputs, and computer-related requirements.

4.3. ESTIMATING DURATION OF CONTACT

As discussed in Section 2, the duration of contact is linked to a particular exposure concentration to estimate exposure. Depending on the purpose of the assessment and the confidence needed in the accuracy of the final estimate, several approaches for obtaining estimates of duration of contact can be used.

Ideally, the time that the individual is in contact with a chemical would be observed and recorded, and linked to the concentrations of the chemical during those time segments. Although it is sometimes feasible to do this (by point-of-contact measurement, see Section 4.1), many times it is not. In those cases, as in concentration characterization, the duration of contact must be estimated by using data that may be somewhat removed from the actual point of contact, and assumptions must be made as to the relevance of the data.

It is common for the estimate of duration of contact at a given concentration to be the single largest source of uncertainty in an exposure assessment.[24] The exposure assessor, in developing or selecting data for making estimates of duration of contact, must often assume that the available data adequately represent exposure.

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[24]Conversely, it may be stated that the largest source of uncertainty is the concentration for a given exposure duration. Often, however, the concentration in the media is known with more certainty than the activities of the individual(s) exposed.

4.3.1. Observation and Survey Data

Observation and recording of activities, including location-time data, are likely to be the types of data collection closest to the point of contact. This can be done by an observer or the person(s) being evaluated for exposure, and can be done for an individual, a population segment, or a population. The usual method for obtaining these data for population segments or populations is survey questionnaires. Surveys can be performed as part of the data-gathering efforts of the exposure assessment, or existing survey data can be used if appropriate.

There are several approaches used in activity surveys, including diaries, respondent or third-party estimates, momentary sampling, videomonitoring, and behavioral meters. The diary approach, probably the most powerful method for developing activity patterns, provides a sequential record of a person's activities during a specified time period. Typical time-diary studies are done across a day or a week. Diary forms are designed to have respondents report all their activities and locations for that period. Carefully designed forms are especially important for diary studies to ensure that data reported by each individual are comparable. The resulting time budget is a sample of activity that can be used to characterize an individual's behavior, activities, or other features during the observation period. Sequential activity monitoring forms the basis of an activity profile. Several studies have demonstrated the reliability of the diary method in terms of its ability to produce similar estimates. One study (Robinson, 1977) found a 0.85 correlation between diary estimates using the yesterday and tomorrow approaches and a 0.86 correlation between overall estimates. However, no definitive study has established the validity of time-diary data. Questionnaires are used for direct questions to collect the basic data needed. Questionnaire design is a complex and subtle process, and should only be attempted with the help of professionals well-versed in survey techniques. A useful set of guidelines is provided in the Survey Management Handbook (U.S. EPA, 1984b).

Respondent estimates are the least expensive and most commonly used questionnaire alternative. Respondents are simply asked to estimate the time they spend at a particular activity. Basically, the question is, how many hours did you spend doing this activity (or in this location or using a certain product)? In exposure studies, respondents may be asked how often they use a chemical or product of interest or perform a specific activity. These data are less precise and likely to be somewhat less accurate than a carefully conducted diary approach.

At a less demanding level, respondents may be asked whether their homes contain items of interest (pesticides, etc.). Since this information is not time-of-activity data, it is more useful in characterizing whether the chemical of interest is present. It does, however, give the assessor some indication that use may or may not occur.

Estimates from other respondents (third parties) use essentially the same approach, except that other informants respond for that individual. Here the question is how many hours per week does the target person spend doing this activity?

Momentary (beeper) sampling or telephone-coincidental techniques ask respondents to give only brief reports for a specific moment — usually the moment the respondent's home telephone or beeper sounds. This approach is limited to times when people are at home or able to carry beepers with them.

Methods that use behavioral meter or monitoring devices are probably the most expensive approach, since they require the use or development of equipment, respondent agreement to use such equipment, and technical help to install or adjust the equipment.

The Exposure Factors Handbook (U.S. EPA, 1989c) contains a summary of published data on activity patterns along with citations. Note that the summary data and the mean values cited are for the data sets included in the Handbook, and may or may not be appropriate for any given assessment.

4.3.2. Developing Other Estimates of Duration of Contact

When activity surveys cannot be used to estimate duration of contact, it may be estimated from more indirect data. This is the least expensive and most commonly used approach for generating estimates of duration of contact; it is also the least accurate. But for some situations, such as assessing the risk to new chemicals being introduced into the marketplace or in assessing future possible uses of contaminated sites, it is the only approach that can be used.

In general, the methods used to make these estimates fall into two areas: (1) those where the time it takes to perform an activity is itself estimated, and (2) those where an average duration of contact is estimated by combining the time of a unit activity with data on the use of a product or commodity.

Methods that try to estimate the time of a particular activity include general time-and-motion studies that might be adapted for use in an exposure assessment, general marketing data which include time of use, anecdotal information, personal experience, and assumptions about the amount of time it takes to perform an activity.

Methods that estimate average times for activities from product or commodity use usually interpret data on product sales or marketing surveys, water use, general food sales, etc. Information on use can be combined with an estimate of the number of persons using the product to estimate the average consumption of the product. If an estimate of the duration of contact with one unit (product, gallon of water, etc.) can be made, this can then be multiplied by the average number of units consumed to arrive at an estimate of average duration of contact for each individual.

Duration-of-contact estimates based on data collected close to the actual point of contact are preferable to those based on indirect measurements; both of these are preferred to estimates based on assumptions alone. This hierarchy is useful in both the data-gathering process and uncertainty analysis.

4.4. OBTAINING DATA ON BODY BURDEN OR BIOMARKERS

Body burden or biomarker data denote the presence of the chemical inside the body of exposed individuals. In a reconstructive assessment, these data, in conjunction with other environmental monitoring data, may provide a better estimate of exposure.

A biomarker of exposure has been defined as an exogenous substance or its metabolite or the product of an interaction between a xenobiotic agent and some target molecule or cell that is measured in a compartment within an organism (NRC, 1989a). Examples of simple direct biomarkers include the chemical itself in body fluid, tissue, or breath. Measurable changes in the physiology of the organism can also constitute markers of exposure. Examples include changes in a particular enzyme synthesis and activity. The interaction of xenobiotic compounds with physiological receptors can produce measurable complexes which also serve as exposure biomarkers. Other markers of exposure include xenobiotic species adducted to protein or DNA, as well as a variety of genotoxicity endpoints, such as micronuclei and mutation. Some biomarkers are specific to a given chemical while others may result from exposure to numerous individual or classes of compounds.

Biomarker data alone do not usually constitute a complete exposure assessment, since these data must be associated with external exposures. However, biomarker data complement other environmental monitoring data and modeling activities in estimating exposure.

4.5. OBTAINING DATA FOR PHARMACOKINETIC RELATIONSHIPS

To estimate dose from exposure, one must understand the pharmacokinetics of the chemical of interest. This is particularly true when comparing risks resulting from different exposure situations. Two widely different exposure profiles for the same chemical may have the same integrated exposure (area under the curve), but may not result in the same internal dose due to variations in disposition of the chemical under the two profiles. For example, enzymes that normally could metabolize low concentrations of a chemical may be saturated when the chemical is absorbed in high doses, resulting in a higher dose delivered to target tissues. The result of these two exposures may even be a different toxicological endpoint, if pharmacokinetic sensitivities are severe enough.

An iterative approach, including both monitoring and modeling, is necessary for proper data generation and analysis. Data collection includes monitoring of environmental media,

personal exposure, biomarkers, and pharmacokinetic data. It may involve monitoring for the chemical, metabolites, or the target biomarker. Monitoring activities must be designed to yield data that are useful for model formulation and validation. Modeling activities must be designed to simulate processes that can be monitored with available techniques. The pharmacokinetic data necessary for model development are usually obtained from laboratory studies with animals. The data are generated in experiments designed to estimate such model parameters as the time course of the process, absorption, distribution, metabolism, and elimination of the chemical. These data, and the pharmacokinetic models developed from them, are necessary to interpret field biomarker data.

4.6. OBTAINING DATA ON INTAKE AND UPTAKE

The Exposure Factors Handbook (U.S. EPA, 1989c) presents statistical data on many of the factors used in assessing exposure, including intake rates, and provides citations for the primary references. Some of these data were developed by researchers using approaches discussed in Section 4.2.1 (for example, Pao et al. [1982] used the diary approach in a study of food consumption). Intake factors included are:

- drinking water consumption rates;
- consumption rates for homegrown fruits, vegetables, beef, and dairy products;
- consumption rates for recreationally caught fish and shellfish;
- incidental soil ingestion rates;
- pulmonary ventilation rates; and
- surface areas of various parts of the human body.

The Exposure Factors Handbook is being updated to encompass additional factors and to include new research data on the factors currently covered. It also provides default parameter values that can be used when site-specific data are not available. Obviously, general default values should not be used in place of known, valid data that are more relevant to the assessment being done.

5. USING DATA TO DETERMINE OR ESTIMATE EXPOSURE AND DOSE

Collecting and assembling data, as discussed in the previous section, is often an iterative process. Once the data are assembled, inferences can be made about exposure concentrations, times of contact, and exposures to persons other than those for whom data are available. During this process, there usually will be gaps in information that can be filled by making a series of assumptions. If these gaps are in areas critical to the accuracy of the assessment, further data collection may be necessary.

Once an acceptable data set[25] is available, the assessor can calculate exposure or dose. Depending on the method used to quantify exposure, there are several ways to calculate exposure and dose. This chapter will discuss making inferences (Section 5.1), assumptions (Section 5.2), and calculations (Section 5.3).

5.1. USE OF DATA IN MAKING INFERENCES FOR EXPOSURE ASSESSMENTS

Inferences are generalizations that go beyond the information contained in a data set. The credibility of an inference is often related to the method used to make it and the supporting data. Anecdotal information is the source of one type of inference, but the assessor has only limited knowledge of how well one anecdote represents the realm of possibilities, so anecdotes as a basis for inference should be used only with considerable caution. Professional judgment is usually preferred to anecdotes assuming that it is based on experience representing a variety of conditions. Statistical inferences also are generalizations that go beyond the data set. They may take any of several forms (see any statistics textbook for examples), but unlike those described above, a statistical inference will usually include a measure of how certain it is. For that reason, statistical inferences are often preferable to anecdotes or professional judgment provided the data are shown to be relevant and adequate.

As discussed above, the primary use of data from exposure-related measurements is to infer more general information about exposure concentrations, contact times, exposures, or doses. For example, measured concentrations in a medium can be used to infer what the concentration might be at the point of contact, which may not have been measured directly. Point-of-contact measurement data for one group of people may be used to infer the exposures of a similar group, or to infer what the exposures of the same group might be at different times.

In all cases, the exposure assessor must have a clear picture of the relationship between the data at hand and what is being characterized by inference. For example, surface water

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[25]An acceptable data set is one that is consistent with the scope, depth, and purpose of the assessment, and is both relevant and adequate as discussed in Section 5.1.

concentration data alone, although essential for characterizing the medium itself, are not necessarily useful for inferring exposures from surface water, since other information is necessary to complete the link between surface water and exposure. But the medium's characteristics (over space and time) can be used, along with the location and activities of individuals or populations, to estimate exposures. Samples taken for exposure assessment may be designed to characterize different aspects (or components) of exposure. For example, a sample taken as a point-of-contact exposure measurement is qualitatively different from a sample of an environmental medium or body fluid.

Different measurements taken under the general category of exposure-related measurements cannot necessarily all be used in the same way. The exposure assessor must explain the relationship between the sample data and the inferences or conclusions being drawn from them. In order to do this, data relevance, adequacy, and uncertainty must be evaluated.

5.1.1. Relevance of Data for the Intended Exposure Assessment

When making inferences from a data set, the assessor must establish a clear link between the data and the inference. When statistically based sampling is used to generate data, relevance is a function of how well the sample represents the medium or parameter being characterized. When planning data collection for an exposure assessment, the assessor can use information about the inferences that will be made to select the best measurement techniques. In many cases data are also available from earlier studies. The assessor must determine (and state) how relevant the available data are to the current assessment; this is usually easier for new data than for previously collected information.

5.1.2. Adequacy of Data for the Intended Assessment

Table 2 in the previous section illustrated how different types of measurements may be used to characterize a variety of concentrations, contact times, and intake or uptake parameters. Nevertheless, just because certain types of measurements generally can be used to make certain inferences, there is no guarantee that this can always be done. The adequacy of the data to make inferences is determined by evaluating the amount of data available and the accuracy of the data. Evaluation of the adequacy of data will ensure that the exposure assessment is conducted with data of known quality.

In general, inadequate data should not be used, but when it can be demonstrated that the inadequacies do not affect results, it is sometimes possible to use such data. In these cases, an explanation should be given as to why the inadequacies do not invalidate conclusions drawn from them. In some cases, even seriously inadequate or only partially relevant data may be the only data available, and some information may be gained from their consideration. It may not be

possible to discard these data entirely unless better data are available. If these data are used, the uncertainties and resulting limitations of the inferences should be clearly stated. If data are rejected for use in favor of better data, the rationale for rejection should be clearly stated and the basis for retaining the selected data should be documented. QA/QC considerations are paramount in considerations of which data to keep and which to discard.

Outliers should not be eliminated from data analysis procedures unless it can be shown that an error has occurred in the sample collection or analysis phases of the study. Very often outliers provide much information to the study evaluators. Statistical tests such as the Dixon test exist to determine the presence of outliers (Dixon, 1950, 1951, 1953, 1960).

5.1.2.1. *Evaluation of Analytical Methods*

Analytical methods are evaluated in order to develop a data set based on validated analytical methods and appropriate QA/QC procedures. In a larger sense, analytical methods can be evaluated to determine the strength of the inferences made from them, and in turn, the confidence in the exposure assessment itself. Consequently, it is just as important to evaluate analytical methods used for data generated under another study as it is to evaluate the methods used to generate new data.

The EPA has established extensive QA/QC procedures (U.S. EPA, 1980). Before measurement data are used in the assessment, they should be evaluated against these procedures and the results stated. If this is not possible, the assessor must consider what effect the unknown quality of the data has on the confidence placed on the inferences and conclusions of the assessment.

5.1.2.2. *Evaluation of Analytical Data Reports*

An assortment of qualifiers is often used in data validation. These qualifiers are used to indicate QA/QC problems such as uncertain chemical identity or difficulty in determining chemical concentration. Qualifiers usually appear on a laboratory analysis report as a letter of the alphabet next to the analytical result. Some examples of data qualifiers, applied by U.S. EPA regional reviewers for Contract Laboratory Program (CLP) data include:

B (blank) - the analyte was found in blank samples;

J (judgment) - the compound is present but the concentration value is estimated;

U (undetected) - the chemical was analyzed for but not detected at the detection limit;

R (reject) - the quality control indicates that the data are unusable.

The exposure assessor may contact the laboratory or the person who validated the data if the definitions of the qualifiers are unclear. Since the exposure assessment is only as good as the

data supporting it, it is essential to interpret these types of data properly to avoid misrepresenting the data set or biasing the results.

5.1.2.2.1. ***Evaluation of censored data sets.*** Exposure assessors commonly encounter data sets containing values that are lower than limits deemed reliable enough to report as numerical values (i.e., quantification limits [QL]). These data points are often reported as nondetected and are referred to as censored. The level of censoring is based on the confidence with which the analytical signal can be discerned from the noise. While the concentration may be highly uncertain for substances below the reporting limit, it does not necessarily mean that the concentration is zero. As a result the exposure assessor is often faced with the problem of having to estimate values for the censored data. Although a variety of techniques have been described in the literature, no one procedure is appropriate under all exposure assessment circumstances; thus, the exposure assessor will need to decide on the appropriate method for a given situation. Techniques for analyzing censored data sets can be grouped into three classes (Helsel, 1990): simple substitution methods, distributional methods, and robust methods.

Simple substitution methods, the most commonly encountered technique, involve substitution of a single value as a proxy for each nondetected data value. Frequently used values have included zero, the QL, QL/2, and QL/$\sqrt{2}$.[26]

In the worst-case approach, all nondetects are assigned the value of the QL, which is the lowest level at which a chemical may be accurately and reproducibly quantitated. This approach biases the mean upward. On the other hand, assigning all nondetects the value of zero biases the mean downward. The degree to which the results are biased will depend on the relative number of detects and nondetects in the data set and the difference between the reporting limit and the measured values above it.

In an effort to minimize the obvious bias introduced by choosing either zero or the QL as the proxy, two other values have been suggested, i.e., QL/2 and QL/$\sqrt{2}$. Assigning all nondetects as QL/2 (Nehls and Akland, 1973) assumes that all values between the QL and zero are equally likely; therefore, an average value would result if many samples in this range were measured. Hornung and Reed (1990) discuss the merits of assigning a value of QL/$\sqrt{2}$ for nondetects rather than QL/2 if the data are not highly skewed (geometric standard deviation < 3.0); otherwise they suggest using QL/2.

Based on reported analyses of simulated data sets that have been censored to varying degrees (Gleit, 1985; Horning and Reed, 1990; Gilliom and Helsel, 1986; Helsel and Cohn,

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[26]Some programs, such as the U.S. Department of Energy (1991), do not recommend this procedure at all, if it can be avoided.

1988), it can be concluded that substitution with QL/2 or QL/$\sqrt{2}$ for nondetects will be adequate for most exposure assessments provided that the nondetects do not exceed 10% to 15% of the data set or the data are not highly skewed. When such situations arise, the additional effort to make use of more sophisticated methods as discussed below is recommended. On the other hand, the exposure assessor may encounter situations in which the purpose of the assessment is only to serve as a screen to determine if a health concern has been triggered or if a more detailed study is required, then assigning the value of the QL to all nondetect values can be justified. If, when using this conservative approach, no concern is indicated, then no further effort is warranted. This method cannot be used to prove an unacceptable risk exists, and any exposure values calculated using this method should be caveated and clearly presented as less than estimates.

Distributional methods, unlike simple substitution methods, make use of the data above the reporting limit to extrapolate below it. One such technique is the use of log-probit analysis. This approach assumes a lognormal probability distribution of the data. In the probit analysis, the detected values are plotted on the scale and the nondetectable values are treated as unknowns, but their percentages are accounted for. The geometric mean is determined from the 50^{th} percentile. As discussed by Travis and Land (1990), limitations of the method have been pointed out, but it is less biased and more accurate than the frequently used substitution methods. This method is useful in situations where the data set contains enough data points above the reporting limit to define the distribution function for the exposure values (i.e., lognormal) with an acceptable degree of confidence. The treatment of the nondetectable samples is then straightforward, assuming the nondetectable samples follow the same distribution as those above the reporting limit.

Robust methods have an advantage over distributional methods in so far as they do not assume that the data above the reporting limit follow a defined distribution (e.g., lognormal) and they are not subject to transformation bias in going from logarithms back to original units. Gilliom and Helsel (1986) have described the application of several approaches to data sets of varying sample size and degree of censoring. These methods involve somewhat more data manipulation than the log-probit method discussed earlier in this Section, but they may be more appropriate to use when the observed data do not fit a lognormal distribution. Generally, these methods only assume a distributional form for the censored values rather than the entire data set, and extrapolation from the uncensored data is done by using regression techniques.

In summary, when dealing with censored data sets, a variety of approaches can be used by the exposure assessor. Selecting the appropriate method requires consideration of the degree of censoring, the goals of the exposure assessment, and the accuracy required. Regardless of the method selected, the assessor should explain the choice made and how it may affect the

summary statistics. Presenting only the summary statistics developed by one of these methods should be avoided. It is always useful to include a characterization of the data by the percentage of detects and nondetects in language such as "in 37% of the samples the chemical was detected above the quantitation limit; of these 37%, the mean concentration was 47 ppm, the standard deviation was 5 ppm, etc."

5.1.2.2.2. ***Blanks and recovery.*** Blank samples should be compared with the results from their corresponding samples. When comparing blank samples to the data set, the following rules should be followed (outlined in Section 3):

- Sample results should be reported only if the concentrations in the sample exceed 10 times the maximum amount detected in the blank for common laboratory contaminants. Common laboratory contaminants include: acetone, 2-butanone (or methyl ethyl ketone), methylene chloride, toluene, and phthalate esters.
- Sample results should be reported only if the concentrations in the sample exceed 5 times the maximum amount detected in a blank for chemicals that are not common laboratory contaminants.

In general, for other types of qualifiers, the exposure assessor may include the data with qualifiers if they indicate that a chemical's concentration is uncertain, but its identity is known. If possible, the uncertainties associated with the qualifier should be noted.

Chemical spike samples that show abnormally high or low recoveries may result in qualified or rejected data. Assessors should not use rejected data; these samples should be treated as if the samples were not taken, since the resulting data are unreliable. Typically, analytical results are reported from the laboratory unadjusted for recovery, with the recovery percentage also reported. The assessor must determine how these data should be used to calculate exposures. If recovery is near 100%, concentrations are not normally adjusted (although the implicit assumption of 100% recovery should be mentioned in the uncertainty section). However, the assessor may need to adjust the data to account for consistent, but abnormally high or low recovery. The rationale for such adjustments should be clearly explained; individual program offices may develop guidance on the acceptable percent recovery limits before data adjustment or rejection is necessary.

5.1.3. Combining Measurement Data Sets From Various Studies

Combining data from several sources into a single data set must be done cautiously. The circumstances under which each set of data was collected (target population, sampling design, location, time, etc.) and quality (precision, accuracy, representativeness, completeness, etc.) must be evaluated. Combining summary statistics of the data sets (e.g., means) into a single set may

be more appropriate than combining the original values. Statistical methods are available for combining results from individual statistical tests. For example, it is sometimes possible to use several studies with marginally significant results to justify an overall conclusion of a statistically significant effect.

The best way to report data is to provide sufficient background information to explain what was done and why, including clear documentation of the source of the data and including any references.

5.1.4. Combining Measurement Data and Modeling Results

Combining model results with measurement data must be done with an understanding of how this affects the resulting inferences, conclusions, or exposure estimates. If model results are used in lieu of additional data points, they must be evaluated for accuracy and representativeness as if they were additional data, and the uncertainty associated with this data combination must be described fully, as discussed in Section 5.1.3.

On the other hand, measurement data are often used within the context of the model itself, as calibration and verification points, or as a check on the plausibility of the model results. If measurements are used within the model, the uncertainty in these measurements affects the uncertainty of the model results, and should be discussed as part of the uncertainty of the model results.

5.2. DEALING WITH DATA GAPS

Even after supplementing existing measurement data with model results, there are likely to be gaps in the information base to be used for calculating exposures and doses. There are several ways to deal with data gaps. None are entirely satisfactory in all situations, but they can be useful depending on the purposes of the assessment and the resources available. The following options can be used singly or in combination:

- New data can be collected. This may be beyond the reach of the assessor's resources, but promises the best chance for getting an accurate answer. It is most likely to be a useful option if the new data are quick and easy to obtain.
- The scope of the assessment can be narrowed. This is possible if the data gaps are in one pathway or exposure route, and the others have adequate data. It may be a viable option if the pathway or route has values below certain bounds, and those bounds are small relative to the other pathways being evaluated. This is unlikely to be satisfactory if the part of the assessment deleted is an important exposure pathway or route and must be evaluated.

- Conservative[27] assumptions can be used. This option is useful for establishing bounds on exposure parameters, but limits how the resulting exposures and doses can be expressed. For example, if one were to assume that a person stays at home 24 hours a day as a conservative assumption, and used this value in calculations, the resulting contact time would have to be expressed as an upper limit rather than a best estimate. When making conservative assumptions, the assessor must be aware of (and explain) how many of these are made in the assessment, and how they influence the final conclusions of the assessment.[28]
- Models may be used in some cases, not only to estimate values for concentrations or exposures, but also to check on how conservative certain assumptions are.
- Surrogate data may also be used in some cases. For example, for pesticide applicators' exposure to pesticides, the EPA Office of Pesticide Programs (U.S. EPA, 1987d) assumes that the general parameters of application (such as the human activity that leads to exposure) are more important than the properties of the pesticide in determining the level of exposure.[29] This option assumes that surrogate data are available and that the differences between the chemical and the surrogate are small. If a clear relationship can be determined between the concentration of a chemical and the surrogate (usually termed an indicator chemical) in a medium, this relationship could also be used to fill data gaps. In any case, the strength and character of the relationship between the chemical and the surrogate must be explained.
- Professional judgment can be used. The utility of this option depends on the confidence placed in the estimate. Expert opinion based on years of observation of similar circumstances usually carries more weight than anecdotal information. The assessor must discuss the implications of these estimates in the uncertainty analysis.

5.3. CALCULATING EXPOSURE AND DOSE

Depending on the approach used to quantify exposure and dose, various types of data will have been assembled. In calculating exposures and doses from these data, the assessor needs to direct attention specifically to certain aspects of the data. These aspects include the use

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[27]"Conservative" assumptions are those which tend to maximize estimates of exposure or dose, such as choosing a value near the high end of the concentration or intake rate range.

[28]Obviously, the mathematical product of several conservative assumptions is more conservative than any single assumption alone. Ultimately, this could lead to unrealistically conservative bounding estimates (see Section 5.3).

[29]Note that when using a passive dosimetry monitoring method, what is measured is the amount of chemical impinging on the skin surface or available for inhalation, that is, exposure, not the actual dose received. Factors such as dermal penetration, are, of course, expected to be highly chemical dependent.

of short-term data for long-term projections, the role of personal monitoring data, and the particular way the data might be used to construct scenarios. Each of these aspects is covered in turn below.

5.3.1. Short-Term Versus Long-Term Data for Population Exposures

Short-term data, for the purposes of this discussion, are data representing a short period of time measured (or modeled) relative to the time period covered in the exposure assessment. For example, a 3-day sampling period would produce short-term data if the exposure assessment covered a period of several years to a lifetime. The same 3-day sampling period would not be considered short-term if the assessment covered, say, a few days to a week.

Short-term data can provide a snapshot of concentrations or exposures during that time, and an inference must be made about what that means for the longer term if the exposure assessment covers a long period. The assessor must determine how well the short-term data represent the longer period.

Even when short-term population data are statistically representative (i.e., they describe the shape of the distribution, the mean, and other statistics), use of these short-term data to infer long-term exposures and risks must be done with caution. Using short-term data to estimate long-term exposures has a tendency to underestimate the number of people exposed, but to overestimate the exposure levels to the upper end of the distribution, even though the mean will remain the same.[30] Both concentration variation at a single point and population mobility will drive the estimates of the levels of exposure for the upper tail of the distribution toward the mean. If short-term data are used for long-term exposure or dose estimates, the implications of this on the estimated exposures must be discussed in the assessment. Likewise, use of long-term monitoring data for specific short-term assessments can miss significant variations due to short-term conditions or activities. Long-term data should be used cautiously when estimating short-term exposures or doses, and the implications should be discussed in the assessment.

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[30]Consider, for example, a hypothetical set of 100 rooms (microenvironments) where the concentration of a particular pollutant is zero in 50 of them, and ranges stepwise from 1 to 50 (nominal concentration units) in the remainder. If one person were in each room, short-term "snapshot" monitoring would show that 50 people were unexposed and the others were exposed to concentrations ranging from 1 to 50. If the concentration in each room remained constant and people were allowed to visit any room at random, long-term monitoring would indicate that all 100 were exposed to a mean concentration of 12.75. The short-term data would tend to overestimate concentration and underestimate the number of persons exposed if applied to long-term exposures. If only average values were available, the long-term data would tend to underestimate concentration and overestimate the number exposed if applied to short-term exposures. Because populations are not randomly mobile or static, the exposure assessor should determine what effect this has on the exposure estimate.

5.3.2. Using Point-of-Contact Data to Calculate Exposure and Dose

Point-of-contact exposure assessments are often done with the intent of protecting the individuals, often in an occupational setting. When exposures are being evaluated to determine whether they exceed an action level or other benchmark, point-of-contact measurements are the most relevant data.

Typically, point-of-contact measurement data reflect exposures over periods of minutes to perhaps a week or so. For individuals whose exposures have been measured, these data may be used directly as an indication of their exposure during the sampling period, provided they are of adequate quality, measure the appropriate chemical, and actually measure exposure while it occurs. This is the only case in which measurement data may be used directly as exposure data.

When using point-of-contact measurements, even with statistically based data, several inferences still must be made to calculate exposure or dose:

- Inferences must be made to apply short-term measurements of exposure to long-term estimates of exposure; these are subject to the cautions outlined in Section 5.3.1.
- Inferences must be made about the representativeness of the individual or persons sampled for the individual or population segment for which the assessment is done.
- Inferences must be made about the factors converting measured exposure to potential or internal dose for use in a risk assessment.
- If the assessment requires it, inferences must be made about the relationship between the measured chemical exposures and the presence and relative contribution of various sources of the chemical.

5.3.3. The Role of Exposure Scenarios in Exposure Assessment

Exposure scenarios have several functions in exposure and risk assessments. First, they are calculational tools to help the assessor develop estimates of exposure, dose, and risk. Whatever combination of data and models is used, the scenario will help the assessor to picture how the exposure is taking place, and will help organize the data and calculations. Second, the estimates derived from scenarios are used to develop a series of exposure and risk descriptors, which were discussed in Section 2.3. Finally, exposure scenarios can often help risk managers make estimates of the potential impact of possible control actions. This is usually done by changing the assumptions in the exposure scenario to the conditions as they would exist after the contemplated action is implemented, and reassessing the exposure and risk. These three uses of exposure assessments are explained in Sections 5.3.3.1, 5.3.3.2, and 5.3.3.3, respectively.

An exposure scenario is the set of information about how exposure takes place. An exposure scenario generally includes facts, data, assumptions, inferences, and sometimes professional judgment about the following:

- The physical setting where exposure takes place (exposure setting)
- The exposure pathway(s) from source(s) to exposed individual(s) (exposure pathways)
- The characterization of the chemical, i.e., amounts, locations, time variation of concentrations, source strength, environmental pathways from source to exposed individuals, fate of the chemical in the environment, etc. (characterization of the chemical)
- Identification of the individual(s) or population(s) exposed, and the profile of contact with the chemical based on behavior, location as a function of time, characteristics of the individuals, etc. (characterization of the exposed population)
- If the dose is to be estimated, assumptions about the transfer of the chemical across the boundary, i.e., ingestion rates, respiration rates, absorption rates, etc. (intake and uptake rates)

It usually is necessary to know whether the effect of concern is chronic, acute, or dependent on a particular exposure time pattern.

The risk characterization, the link between the development of the assessment and the use of the assessment, is usually communicated in part to the risk manager by means of a series of "risk descriptors," which are merely different ways to describe the risk. Section 2.3 outlined two broad types of descriptors: individual risk descriptors and population risk descriptors, with several variations for each. To the exposure or risk assessor, different types of risk information require different risk descriptors and different analyses of the data. The following paragraphs discuss some of the aspects of developing and using exposure scenarios in various functions for exposure assessment.

5.3.3.1. *Scenarios as a Means to Quantify Exposure and Dose*

When using exposure scenario evaluation as a means to quantify exposure and dose, it is possible to accumulate a large volume of data and estimated values, and both the amount and type of information can vary widely. The exposure scenario also contains the information needed to calculate exposure, since the last three bullets above (Section 5.3.3) are the primary variables in most exposure and dose equations.

As an example, consider Equation 2-5, the equation for lifetime average daily potential dose ($LADD_{pot}$). This equation uses the variables of exposure concentration (C), intake rate (IR), and exposure duration (ED) as the three primary variables. Body weight (BW) and averaging time (AT) (in this case, lifetime, LT) are not related to the exposure or dose *per se,* but are averaging variables used to put the resulting dose in convenient units of lifetime average exposure or dose per kg of body weight.

In looking at the three primary variables (C, IR, and ED), the exposure assessor must determine what value to use for each to solve the equation. In actuality, the information available for a variable like C may consist of measurements of various points in an environmental medium, source and fate characterizations, and model results. There will be uncertainty in the values for C for any individual; there will also be variability among individuals. Each of these primary variables will be represented by a range of values, even though at times, the boundaries of this range will be unknown. How exposure or dose is calculated depends on how these ranges are treated.

In dealing with these ranges in trying to solve the equation for LADD, the assessor has at least two choices. First, statistical tools, such as the Monte Carlo analysis, can be used to enter the values as frequency distributions, which results in a frequency distribution for the LADD. This is an appropriate strategy when the frequency distributions are known for C, IR, and ED (or for the uptake analogs, C, K_p, SA, and ED introduced in Section 2), and when these variables are independent.

A second approach is to select or estimate discrete values from the ranges of each of the variables and use these values to solve the LADD equation. This approach usually results in a less certain estimate, but may be easier to do. Which values are used determines how the resulting estimate will be described. Several terms for describing such estimates are discussed in Section 5.3.3.2.

Since exposure to chemicals occurs through a variety of different pathways, contact patterns, and settings, sufficient perspective must be provided to the users of the assessment (usually risk managers) to help them make an informed decision. Providing this perspective and insight would be relatively straightforward if complete and accurate information were known about the exposure, dose, and risk for each and every person within the population of interest. In this hypothetical situation, these individual data could actually be arrayed next to the name of each person in the population, or the data could be compiled into frequency distribution curves. From such distributions, the average, median, maximum, or other statistical values could easily be read off the curves and presented to the risk manager. In addition, accurate information could be provided about how many persons are above certain exposure, dose, or risk levels as well as information about where various subgroups fall within the subject distribution.

Unfortunately, an assessor rarely has these kinds of data; the reality an assessor faces usually falls far short of this ideal. But it is precisely this kind of information about the distribution of exposure, dose, and risk that is needed many times by the risk assessor to characterize risk, and by the risk manager to deal with risk-related issues.

In the absence of comprehensive data, or if the scenario being evaluated is a possible future use or post-control scenario, an assessor must make assumptions in order to estimate what

the distribution would look like if better data were available, or if the possible future use becomes a reality. Communicating this estimated distribution to the risk manager can be difficult. The assessor must not only estimate exposure, dose, and risk levels, but must also estimate where those levels might fall on the actual distributions or estimated distributions for potential future situations. To help communicate where on the distribution the estimate might fall, loosely defined terms such as reasonable worst case, worst case, and maximally exposed individual have been used by assessors. Although these terms have been used to help describe the exposure assessor's perceptions of where estimated exposures fall on the actual or potential distribution for the future use, the *ad hoc* nature of the historical definitions used has led to some inconsistency. One of the goals of these Guidelines is to promote greater consistency in the use of terms describing exposure and risk.

5.3.3.2. *Exposure Scenarios and Exposure Estimators as Input to Risk Descriptors*

As discussed in Section 2.3, risk descriptors convey information about risk to users of that information, primarily risk managers. This information usually takes the form of answers to a relatively short set of questions, not all of which are applicable to all assessments. Section 5.3.5 provides more detail on how the exposure assessor's analysis leads to construction of the risk descriptors.

5.3.3.3. *Exposure Scenarios as a Tool for Option Evaluation*

A third important use for exposure scenarios is as a tool for evaluating proposed options for action. Risk managers often have a number of choices for dealing with environmental problems, from taking no action on one extreme to a number of different actions, each with different costs, on the other. Often the exposure scenarios developed as part of the baseline risk assessment provide a powerful tool to evaluate the potential reduction of exposure and risk for these various options, and consequently are quite useful in many cost-benefit analyses.

There are several additional related uses of exposure scenarios for risk managers. They may help establish a range of options for cleanup by showing the sensitivity of the risk estimates to the changes in assumed source or exposure levels. The exposure assessor can use the sensitivity analysis of the exposure scenario to help evaluate and communicate the uncertainty of the assumptions, and what can be done to reduce that uncertainty. Well-crafted and soundly based exposure scenarios may also help communicate risks and possible options to community groups.

Although it is beyond the scope of these Guidelines to detail the methods used for option evaluation and selection, the assessor should be aware of this potential use. Discussing strategy

(and specific information needs) with risk managers is usually prudent before large resource expenditures are made in the risk assessment area.

5.3.4. General Methods for Estimating Exposure and Dose

A variety of methods are used to obtain estimates of dose necessary for risk characterization. These range from quick screening level calculations and rules of thumb to more sophisticated techniques. The technique to be used in a given case is a matter of the amount of information available and the purpose of the assessment. Several of the methods are outlined in the following sections.

Normally it is neither practicable nor advisable to immediately develop detailed information on all the potential pathways, since not all may contribute significantly to the outcome of the assessment.[31] Rather, evaluation of the scenario is done in an iterative manner. First, screening or bounding techniques are used to ascertain which pathways are unimportant, then the information for the remaining pathways is refined, iteratively becoming more accurate, until the quantitative objectives of the assessment are met (or resources are depleted).

In beginning the evaluation phase of any assessment, the assessor should have a scenario's basic assumptions (setting, scope, etc.) well identified, one or more applicable exposure pathways defined, an equation for evaluating the exposure or dose for each of those exposure pathways, and the data and information requirements pertinent to solving the equations. Quality and quantity of data and information needed to substitute quantitative values or ranges into the parameters of the exposure equation will often vary widely, from postulated assumptions to actual high-quality measurements. Many times, there are several exposure pathways identified within the scenario, and the quality of the data and information may vary for each.

A common approach to estimating exposure and dose is to do a preliminary evaluation, or screening step, during which bounding estimates are used, and then to proceed to refine the estimates for those pathways that cannot be eliminated as of trivial importance.

5.3.4.1. *Preliminary Evaluation and Bounding Estimates*

The first step that experienced assessors usually take in evaluating the scenario involves making bounding estimates for the individual exposure pathways. The purpose of this is to eliminate further work on refining estimates for pathways that are clearly not important.

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[31]There are some important exceptions to this statement. First, the public or other concerned groups may express particular interest in certain pathways, which will not normally be dropped entirely at this point. Second, for routine repetitive assessments using a certain standard scenario for many chemicals, once the general bounding has been done on the various possible pathways, it may become standard operating procedure to immediately begin developing information for particular pathways as new chemicals are assessed.

The method used for bounding estimates is to postulate a set of values for the parameters in the exposure or dose equation that will result in an exposure or dose higher than any exposure or dose expected to occur in the actual population. The estimate of exposure or dose calculated by this method is clearly outside of (and higher than) the distribution of actual exposures or doses. If the value of this bounding estimate is not significant, the pathway can be eliminated from further refinement.[32]

The theoretical upper bounding estimate (TUBE) is a type of bounding estimate that can be easily calculated and is designed to estimate exposure, dose, and risk levels that are expected to exceed the levels experienced by all individuals in the actual distribution. The TUBE is calculated by assuming limits for all the variables used to calculate exposure and dose that, when combined, will result in the mathematically highest exposure or dose (highest concentration, highest intake rate, lowest body weight, etc.). The theoretical upper bound is a bounding estimate that should, if the limits of the parameters used are known, ensure that the estimate is above the actual exposures received by all individuals in the population. It is not necessary to go to the formality of the TUBE to assure that the exposure or dose calculated is above the actual distribution, however, since any combination that results in a value clearly higher than the actual distribution can serve as a suitable upper bound.

The bounding estimate (a limit of individual exposure, dose or risk) is most often used only to eliminate pathways from further consideration. This is often done in screening-level assessments, where bounding estimates of exposure, dose, or risk provide a quick and relatively easy check on whether the levels to be assessed are trivial relative to a level that would cause concern. If acceptably lower than the concern level, then additional assessment work is not necessary.

Bounding estimates also are used in other types of assessments. They can be used for deregulation of chemicals when pathways or concentrations can be shown to present insignificant or *de minimis* risk. They can be used to determine whether more information is needed to determine whether a pathway is significant; if the pathway's significance cannot be ruled out by a bounding estimate, test data may be needed to refine the estimate.

There are two important points about bounding estimates. First, the only thing the bounding estimate can establish is a level to eliminate pathways from further consideration. It cannot be used to make a determination that a pathway is significant (that can only be done after more information is obtained and a refinement of the estimate is made), and it certainly cannot

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[32]"Not significant" can mean either that it is so small relative to other pathways that it will not add perceptibly to the total exposure being evaluated or that it falls so far below a level of concern that even when added to other results from other pathways, it will be trivial. Note that a "level of concern" is a risk management term, and the assessor must discuss and establish any such levels of concern with risk managers (and in some cases, concerned groups such as the local community) before eliminating pathways as not significant.

be used for an estimate of actual exposure (since by definition it is clearly outside the actual distribution). Second, when an exposure scenario is presented in an assessment, it is likely that the amount of refinement of the data, information, and estimates will vary by pathway, some having been eliminated by bounding estimates, some eliminated after further refinement, and others fully developed and quantified. This is an efficient way to evaluate scenarios. In such cases, bounding estimates must not be considered to be equally as sophisticated as an estimate of a fully developed pathway, and should not be described as such.

Experienced assessors can often eliminate some obvious pathways more or less by inspection as they may have evaluated these pathways many times before.[33] In these cases, the assessor must still explain why the pathway is being eliminated. For less experienced assessors, developing bounding estimates for all pathways is instructive and will be easier to defend.

5.3.4.2. *Refining the Estimates of Exposure and Dose*

For those pathways not eliminated by bounding estimates or judged trivial, the assessor will then evaluate the resulting exposure or dose. At this point, the assessor will make estimates of exposure or dose that are designed to fall on the actual distribution. The important point here is that unlike a bounding estimate, these estimates of exposure or dose should focus on points in the actual distribution. Both estimates of central tendency and estimates of the upper end of the distribution curve are useful in crafting risk descriptors.

Consider Equation 2-6 for the lifetime average daily potential dose ($LADD_{pot}$), an equation often used for linear, nonthreshold carcinogen risk models. The assessor will use the data, ranges of data, distributions of data, and assumptions about each of the factors needed to solve the equation for dose. Generally, both central estimates and high-end estimates are performed. Each of these estimates has uncertainty (perhaps unquantifiable uncertainty), and the better the quality and comprehensiveness of data used as input to the equation, the less uncertainty.

After solving the equation, the assessor will determine whether the uncertainty associated with the answer is sufficiently narrow to allow the risk descriptors to be developed (see Section 3.4) and to answer satisfactorily the questions posed in the exposure assessment statement of purpose. Evaluating whether the data, uncertainty, risk descriptors, and answers to the questions are good enough is usually a joint responsibility of the risk assessor and the risk manager.

Should the estimates of exposure or dose have sufficiently narrow uncertainty, the assessor can then proceed to develop the descriptors and finish the assessment. If not, the data or assumptions used usually will have to be refined, if resources allow, in an attempt to bring the

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[33]Experienced assessors may also be able to determine quickly that a pathway requires refined estimation.

estimated exposure or dose closer to what the assessor believes are the actual values in the population. Refining the estimates usually requires that new data be brought into consideration;[34] this new information can be other studies from the literature, information previously developed for another, related purpose that can be adapted, or new survey, laboratory, or field data. The decision about which particular parts of the information base to refine should be based both on which data will most significantly reduce the uncertainty of the overall exposure or dose estimate, and on which data are in fact obtainable either technologically or within resource constraints.

After refinement of the estimate, the assessor and risk manager again determine whether the estimates provided will be sufficient to answer the questions posed to an acceptable degree, given the uncertainties that may be associated with those estimates. Refinements proceed iteratively until the assessment provides an adequate answer within the resources available.

5.3.5. Using Estimates for Developing Descriptors

Risk assessors and risk managers are encouraged to explore a range of ways to describe exposure and risk information, depending on the purpose of the assessment and the questions for which the risk manager must have answers. Section 2.3 outlines a series of risk descriptors; in the sections below, these are discussed in the context of how an exposure assessor's analysis of the data would lead to various descriptors for risk.

5.3.5.1. *Individual Exposure, Dose, and Risk*

Questions about individual risk are an important component of any assessment, especially an estimate of the high end of the distribution. Section 5.3.4.1 indicated that bounding estimates are actually a useful but limited form of individual risk estimate, a form which is by definition beyond the highest point on the population distribution. This section deals with estimates that are actually on the distribution of exposure, dose, or risk.

There are several approaches for arriving at an individual risk estimate. Since calculation of risk involves using information from fields other than exposure assessment, the reader is advised to consult other Agency guidelines for more detailed discussions (e.g., U.S. EPA, 1986b, 1986c, 1988b, 1988c, 1991a). The uncertainty in the risk estimate will depend heavily on the quality of the information used. There are several steps in the process:

First, the question of unusual susceptibility of part of the population must be addressed. If equal doses result in widely different responses in two individuals, it may be necessary to consult with scientists familiar with the derivation of the dose-response relationship for the

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[34]It also can involve new methods or additional methods for analyzing the old data.

chemical in question in order to ascertain whether this is normal variability among members of a population. Normal variability should have been considered as part of the development of the dose-response relationship; unusual susceptibility may not have been. If such a highly susceptible subgroup can be identified, it is often useful to assess their risk separately from the general population. It will not be common, given the current data availability, to clearly identify such susceptible subgroups. If none can be identified, the default has usually been to assume the dose-response relationship applies to all members of the population being assessed. Where no information shows the contrary, this assumption may be used provided it is highlighted as a source of uncertainty.

Second, after the population or population segment can be represented by a single dose-response relationship, the appropriate dose for use in the dose-response relationship (absorbed/internal dose, potential dose, applied dose, effective dose) must be identified. For dose-response relationships based on administered dose in animal studies, potential dose will usually be the human analogue. If the dose-response relationship is based on internal dose, then that is the most appropriate human dose. If the estimates of exposure and dose from the exposure assessment are in an inappropriate form (say, potential dose rather than internal dose), they must be converted before they are used for risk calculations. This may involve analysis of bioavailability, absorption rates as a function of form of the chemical and route, etc. If these data are not available, the default has been to assume the entire potential dose becomes the internal dose.[35] As more data become available concerning absorption for different chemicals, this conservative assumption may not always be the best, or even a credible, default. Whatever assumption is made concerning absorption (or the relationships among any of the different dose terms if used, for that matter), it should be highlighted in the uncertainty section.

Once the first two steps have been done, and the dose-response relationship and type of dose have been identified, the exposure and dose information needs to be put in the appropriate form. Ideally, this would be a distribution of doses of the appropriate type across the population or population subgroup of interest. This may involve converting exposures into potential doses or converting potential doses into internal, delivered, or biologically effective doses. Once this is accomplished, the high-end estimate of dose will often (but not always) lead fairly directly to the high-end estimate of risk. The method used to develop the high-end estimate for dose

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[35]The unstated assumption is often made that the relationship between administered dose and absorbed dose in the animal is the same as that between potential dose and internal dose in humans, provided a correction is made for body weight/surface area. In other words, the bioavailability and absorption fractions are assumed to be the same in the human as in the animal experiment. If no correction is made for absorption, this leads to the assumption that the absorption percent is *the same as in the animal experiment from which the dose-response relationship was derived.* Note this uncorrected conversion of potential dose to internal dose does not assume "100% absorption" unless there was 100% absorption in the animal study.

depends on the data available. Because of the skewed nature of exposure data, there is no exact formula that will guarantee an estimate will fall into this range in the actual population if only sparse data are available.

The high-end risk is a plausible estimate of the individual risk for those persons at the upper end of the risk distribution. The intent of this descriptor is to convey an estimate of risk in the upper range of the distribution, but to avoid estimates that are beyond the true distribution. Conceptually, high-end risk means risks above the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest risk. This descriptor is intended to estimate the risks that are expected to occur in small but definable high-end segments of the subject population. The use of "above the 90th percentile" in the definition is not meant to precisely define the range of this descriptor, but rather to clarify what is meant conceptually by high end.

The high-end segments of the exposure, dose, and risk populations may represent different individuals. Since the location of individuals on the exposure, dose, and risk distributions may vary depending on the distributions of bioavailability, absorption, intake rates, susceptibility, and other variables, a high exposure does not necessarily result in a high dose or risk, although logically one would expect a moderate to highly positive correlation among exposure, dose, and risk.

When the complete data on the population distributions of exposures and doses are available, and the significance of the factors above (bioavailability, etc.) are known to the extent to allow a risk distribution to be constructed, the high-end risk estimate can be represented by reporting risks at selected percentiles of the distributions, such as the 90th, 95th, or 98th percentile. When the complete distributions are not available, the assessor should conceptually target something above the 90th percentile on the actual distribution.

In developing estimates of high-end individual exposure and dose, the following conditions must be met:

- The estimated exposure or dose is on the expected distribution, not above the value one would expect for the person with the highest estimated risk in the population. This means that when constructing this estimate from a series of factors (environmental concentrations, intake rates, individual activities, etc.), not all factors should be set to values that maximize exposure or dose, since this will almost always lead to an estimate that is much too conservative.
- The combination of values assigned to the exposure and dose factors can be expected to be found in the actual population. In estimating high-end exposures or doses for

future use or post-control scenarios, the criterion to be used should be that it is expected to be on the distribution provided the future use or control measure occurs.[36]

Some of the alternative methods for determining a high-end estimate of dose are:

- If sufficient data on the distribution of doses are available, take the value directly for the percentile(s) of interest within the high end. If possible, the actual percentile(s) should be stated, or the number of persons determined in the high end above the estimate, in order to give the risk manager an idea of where within the high end-range the estimate falls.
- If data on the distribution of doses are not available, but data on the parameters used to calculate the dose are available, a simulation (such as an exposure model or Monte Carlo simulation) can sometimes be made of the distribution. In this case, the assessor may take the estimate from the simulated distribution. As in the method above, the risk manager should be told where in the high-end range the estimate falls by stating the percentile or the number of persons above this estimate. The assessor and risk manager should be cautioned that unless a great deal is known about exposures or doses at the high end of the distribution, simulated distributions may not be able to differentiate between bounding estimates and high-end estimates. Simulations often include low-probability estimates at the upper end that are higher than those actually experienced in a given population, due to improbability of finding these exposures or doses in a specific population of limited size, or due to nonobvious correlations among parameters at the high ends of their ranges.[37] Using the highest estimate from a Monte Carlo simulation may therefore overestimate the exposure or dose for a specific population, and it is advisable to use values somewhat less than the highest Monte Carlo estimated value if one is to defend the estimate as being within the actual population distribution and not above it.

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[36]This means that estimates of high-end exposure or dose for future uses are limited to the same conceptual range as current uses. Although a "worst-case" combination of future conditions or events may result in an exposure that is conceivably possible, the assessor should not merely use a worst-case combination as an estimate of high-end exposure for possible future uses. Rather, the assessor must use judgment as to what the range of exposures or doses would plausibly be, given the population size and probability of certain events happening.

[37]For example, although concentration breathed, frequency, duration, and breathing rate may be independent for a consumer painting rooms in a house under most normal circumstances, if the concentration is high enough, it may affect the other parameters such as duration or breathing rate. These types of high-end correlations are difficult to quantify, and techniques such as Monte Carlo simulations will not consider them unless relationships are known and taken into account in the simulation. If extreme concentration in this case resulted in lower breathing rate or duration, a noncorrected Monte Carlo simulation could overestimate the exposure or dose at the high end. Far less likely, due to self-preservation processes, would seem the case where high concentration increases duration or intake rate, although this theoretically might also occur.

Simulations using finite ranges for parameters will result in a simulated distribution with a calculable finite maximum exposure, and the maximum exposures calculated in repeated simulations will not exceed this theoretical maximum.[38] When unbounded default distributions, such as lognormal distributions, are used for input parameters to generate the simulated exposure distributions, there will not be a finite maximum exposure limit for the simulation, so the maximum value of the resulting simulated distribution will vary with repeated simulations. The EPA's Science Advisory Board [SAB] (U.S. EPA, 1992a) has recommended that values above a certain percentile in these simulations be treated as if they were bounding estimates, not estimates of high-end exposures (see Figure 2). The SAB noted that for large populations, simulated exposures, doses, and risks above the 99.9th percentile may not be meaningful when unbounded lognormal distributions are used as a default.

Although the Agency has not specifically set policy on this matter, exposure assessors should observe the following caution when using simulated distributions. The actual percentile cutoff above which a simulation should be considered a *bounding estimate* may be expected to vary depending on the size of the population. Since bounding estimates are established to develop statements that exposures, doses, and risks are "not greater than...," it is prudent that the percentile cutoff bound expected exposures for the size of the population being evaluated. For example, if there are 100 persons in the population, it may be prudent to consider simulated exposures above the 1 in 500 level or 1 in 1000 level (i.e., above the 99.5th or 99.9th percentile, respectively) to be bounding estimates. Due to uncertainties in simulated distributions, assessors should be cautious about using estimates above the 99.9th percentile for estimates of *high-end* exposure regardless of the size of the population. The Agency or individual program offices may issue more direct policy for setting the exact cutoff value for use as high-end and bounding estimates in simulations.

- If some information on the distribution of the variables making up the exposure or dose equation (e.g., concentration, exposure duration, intake or uptake rates) is available, the assessor may estimate a value which falls into the high end by meeting the defining criteria of "high end": an estimate that will be within the distribution, but high enough so that less than 1 out of 10 in the distribution will be as high. The assessor often constructs such an estimate by using maximum or near-maximum values for one or more of the most sensitive variables, leaving others at their mean

[38]This maximum is the theoretical upper bounding estimate (TUBE).

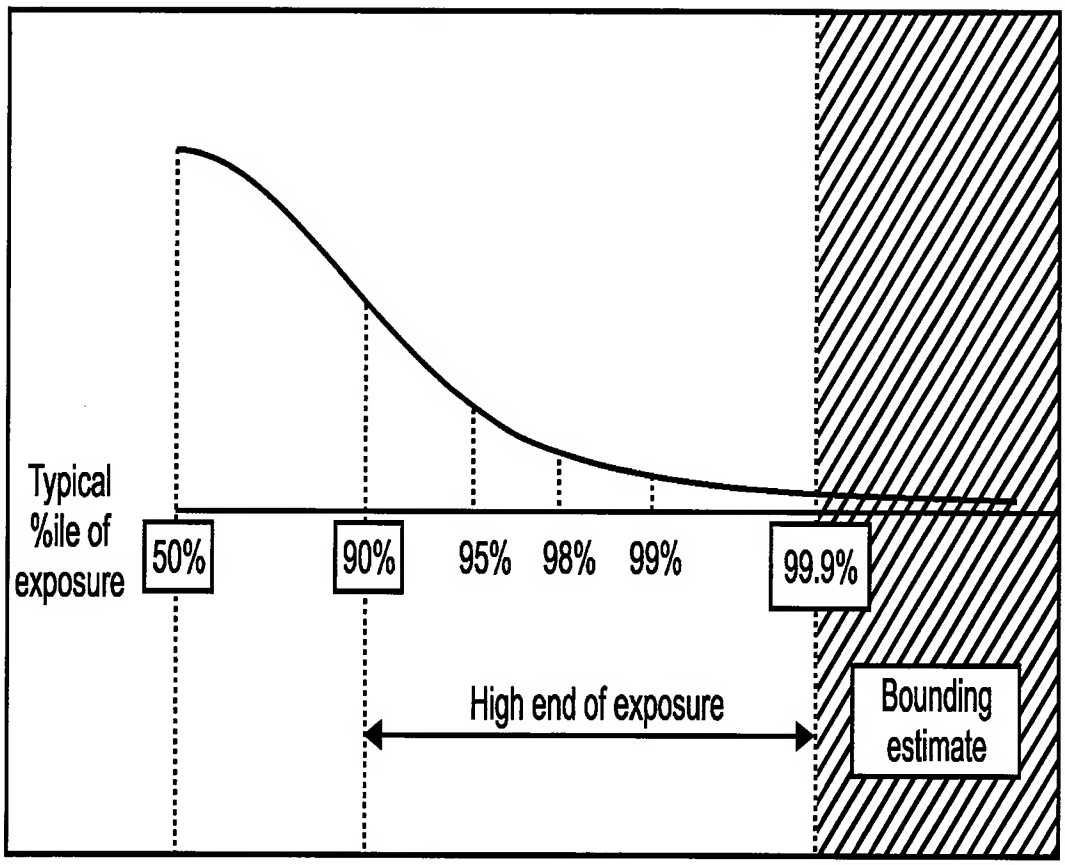

Figure 2. Schematic of exposure estimators for unbounded simulated population distributions.

values.[39] The exact method used to calculate the estimate of high-end exposure or dose is not critical; it is very important that the exposure assessor explain why the estimate, in his or her opinion, falls into the appropriate range, not above or below it.

- If almost no data are available, it will be difficult, if not impossible, to estimate exposures or doses in the high end. One method that has been used, especially in screening-level assessments, is to start with a bounding estimate and back off the limits used until the combination of parameter values is, in the judgment of the assessor, clearly in the distribution of exposure or dose. Obviously, this method results in a large uncertainty. The availability of pertinent data will determine how easily and defensibly the high-end estimate can be developed by simply adjusting or backing off from the ultra conservative assumptions used in the bounding estimates. This estimate must still meet the defining criteria of "high end," and the assessor should be ready to explain why the estimate is thought to meet the defining criteria.

A descriptor of central tendency may be either the arithmetic mean risk (average estimate) or the median risk (median estimate), but should be clearly labeled as such. Where both the arithmetic mean and the median are available, but differ substantially, it is helpful to present both.

Exposure and dose profiles often fall in a skewed distribution that many times appears to be approximately lognormally distributed, although statistical tests for lognormality may fail. The arithmetic mean and the median are the same in a normal distribution, but exposure data are rarely normally distributed. As the typical skewness in the distribution increases, the exposure or dose distribution comes to resemble a lognormal curve where the arithmetic mean will be higher than the median. It is not unusual for the arithmetic mean to be located at the 75th percentile of the distribution or higher. Thus, the arithmetic mean is not necessarily a good indicator of the midpoint (median, 50th percentile) of a distribution.

The average estimate, used to describe the arithmetic mean, can be approximated by using average values for all the factors making up the exposure or dose equation. It does not necessarily represent a particular individual on the distribution, but will fall within the range of the actual distribution. Historically, this calculation has been referred to as the average case, but as with other *ad hoc* descriptors, definitions have varied widely in individual assessments.

When the data are highly skewed, it is sometimes instructive to approximate the median exposure or dose, or median estimate. This is usually done by calculating the geometric mean of the exposure or dose distribution, and historically this has often been referred to as the typical

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[39]Maximizing all variables, as is done in bounding estimates, will result in virtually all cases in an estimate that is above the bounds of this range, that is, above the actual values seen in the population.

case, although again, definitions have varied widely. Both the average estimate and median estimate are measures of the central tendency of the exposure or dose distribution, but they must be clearly differentiated when presenting the results.

It will often be useful to provide additional specific individual risk information to provide perspective for the risk manager. This specific information may take the form of answers to what if questions, such as, what if a consumer should use this product without adequate ventilation? For the risk manager, these questions are likely to put bounds on various aspects of the risk question. For the assessor, these are much less complicated problems than trying to estimate baseline exposure or dose in an actual population, since the answers to these questions involve choosing values for various parameters in the exposure or risk equations and solving them for the estimate.

This type of risk descriptor is a calculation of risk to specific hypothetical or actual combinations of factors postulated within the exposure assessment. It is often valuable to ask and answer specific questions of the "what if" nature to add perspective to the risk assessment.

Each assessment may have none, one, or several of these specific types of descriptors. The answers to these questions might be a point estimate or a range, but are usually fairly simple to calculate. The answers to these types of postulated questions, however, do not directly give information about how likely that combination of values might be in the actual population, so there are some limits to the applicability of these descriptors.

5.3.5.2. *Population Exposure, Dose, and Risk*

Questions about population exposure, dose, and risk are central to any risk assessment. Ideally, given the time and methods, the assessor might strive to construct a picture of exposure, dose, and risk in which each individual exposure, dose and risk is known. These data could then be displayed in a frequency distribution.

The risk manager, perhaps considering what action might be necessary for this particular situation, might ask how many cases of the particular effect might be probabilistically estimated in a population during a specific time period, or what percentage of the population is (or how many people are) above a certain exposure, dose, or risk level.

For those who do the assessments, answering these questions requires some knowledge of the population frequency distribution. This information can be obtained or estimated in several ways, leading to two descriptors of population risk.

The first is the probabilistic number of health effect cases estimated in the population of interest over a specified time period. This descriptor can be obtained either by summing the individual risks over all the individuals in the population, or by multiplying the slope factor obtained from a carcinogen dose-response relationship, the arithmetic mean of the dose, and the

size of the population. The latter approach may be used only if the risk model assumes a single linear, nonthreshold response to dose, and then only with some caution.[40] If risk varies linearly with dose, knowing the arithmetic mean risk and the population size can lead to an estimate of the extent of harm for the population as a whole, excluding sensitive subgroups for which a different dose-response curve may need to be used. For noncarcinogens, or for nonlinear, nonthreshold carcinogen models, using the arithmetic mean exposure or dose, multiplying by a slope factor to calculate an average risk, and multiplying by the population size is not appropriate, and risks should be summed over individuals.[41]

Obviously, the more relevant information one has, the less uncertain this descriptor, but in any case, the estimate used to develop the descriptor is also limited by the inherent uncertainties in risk assessment methodology, e.g., the risk estimates often being upper confidence level bounds. With the current state of the science, this descriptor should not be confused with an actuarial prediction of cases in the population (which is a statistical prediction based on a great deal of empirical data).

The second type of population risk descriptor is an estimate of the percentage of the population, or the number of persons, above a specified level of risk, RfD, RfC, LOAEL, or other specific level of interest. This descriptor must be obtained by measuring or simulating the population distribution, which can be done in several ways.

First, if the population being studied is small enough, it may be possible to measure the distribution of exposure or dose. Usually, this approach can be moderately to highly costly, but it may be the most accurate. Possible problems with this approach are lack of measuring techniques for the chemical of interest, the availability of a suitable population subset to monitor, and the problem of extrapolating short-term measurements to long-term exposures.

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[40]For example, when calculating risks using doses and "slope factors," the risk is approximately linear with dose until relatively high individual risks (about 10^{-1}) are attained, after which the relationship is no longer even approximately linear. This results from the fact that no matter how high the dose, the individual risk cannot exceed 1, and the dose-risk curve approaches 1 asymptotically. This can result in artifacts when calculating population risk from average individual doses and population size if there are individuals in the population in this nonlinear risk range. Consider a population of five persons, only one of whom is exposed. As an example, assume a lifetime average daily dose of 100 mg/kg/day corresponds to an individual risk of 4×10^{-1}. Increasing the dose fivefold, to 500 mg/kg/day, would result in a higher individual risk for that individual, but due to the nonlinearity of the dose-risk curve, not yet a risk of 1. The average dose for the five persons in the population would then be 100 mg/kg/day. Multiplying the "average risk" of 4×10^{-1} by the population size of five results in an estimate of two cases, even though in actuality only one person is exposed. Although calculating average individual dose, estimating individual risk from it, and multiplying by the population size is a useful approximation if all members of the population are within the approximately linear range of the dose-risk curve, this method should not be used if some members of the population have calculated individual risks higher than about 10^{-1}, since it will overestimate the number of cases.

[41]In these cases, a significant problem can be the lack of a constant (or nearly constant) "slope factor" that would be appropriate over a wide exposure/dose range, since the dose-response curve may have thresholds, windows, or other discontinuities.

Second, the distribution itself may be simulated from a model such as an exposure model (a model that reports exposures or doses by linking concentrations with contact times for subsets of the population, such as those living various distances from a source) or a Monte Carlo simulation. Although this may be considerably less costly than measurements, it will probably be less accurate, especially near the high end of the distribution. Although models and statistical simulations can be fairly accurate if the proper input data are available, these data are often difficult to obtain and assumptions must be made; use of assumptions may reduce the certainty of the estimated results.

Third, it may be possible to estimate how many people are above a certain exposure, dose, or risk level by identifying and enumerating certain population segments known to be at higher exposure, dose, sensitivity, or risk than the level of interest.

For those who use the assessments, this descriptor can be used in the evaluation of options if a level can be identified as an exposure, dose, or risk level of concern. The options can then be evaluated by estimating how many persons would go from the higher category to the lower category after the option is implemented.

Questions about the distribution of exposure, dose, and risk often require the use of additional risk descriptors. In considering the risks posed by the particular situation being evaluated, a risk manager might want to know how various subgroups fall within the distribution, and if there are any particular subgroups at disproportionately high risk.

It is often helpful for the risk assessor to describe risk by an identification, and if possible, characterization and quantification of the magnitude of the risk for specific highly exposed subgroups within the population. This descriptor is useful when there is (or is expected to be) a subgroup experiencing significantly different exposures or doses from that of the larger population.

It is also helpful to describe risk by an identification, and if possible, characterization and quantification of the magnitude of risk for specific highly sensitive or highly susceptible subgroups within the population. This descriptor is useful when the sensitivity or susceptibility to the effect for specific subgroups within the population is (or is expected to be) significantly different from that of the larger population. In order to calculate risk for these subgroups, it will sometimes be necessary to use a different dose-response relationship.

Generally, selection of the subgroups or population segments is a matter of either *a priori* interest in the subgroup, in which case the risk manager and risk assessor can jointly agree on which subgroups to highlight, or a matter of discovery of a subgroup during the assessment process. In either case, the subgroup can be treated as a population in itself and characterized the same way as the larger population using the descriptors for population and individual risk.

Exposures and doses for highly-exposed subpopulations can be calculated by defining the population segment as a population, then estimating the doses as for a population. The assessor must make it clear exactly which population was considered.

A special case of a subpopulation is that of children. For exposures that take place during childhood, when low body weight results in a higher dose rate than would be calculated using the $LADD_{pot}$ (Equation 2-6), it is appropriate to average the dose rate (intake rate/body weight) rather than dose. The $LADD_{pot}$ equation then becomes

$$LADD_{pot} = \sum_i [\, \bar{C}_i \cdot (\bar{IR} / BW)_i \cdot (ED_i / LT) \,] \qquad (5\text{-}1)$$

where $LADD_{pot}$ is the lifetime average daily potential dose, ED_i is the exposure duration (time over which the contact actually takes place), $\bar{C}_i$ is the average exposure concentration during period of calendar time ED_i, $\bar{IR}_i$ is the average ingestion or inhalation rate during ED_i, BW_i is body weight during exposure duration ED_i, and LT is the averaging time, in this case, a lifetime (converted to days). This form of the $LADD_{pot}$ equation, if applied to an exposure that occurs primarily in childhood (for example, inadvertent soil ingestion), may result in an $LADD_{pot}$ calculation somewhat higher than that obtained by using Equation 2-6, but there is some evidence that it is more defensible (Kodell et al., 1987; additional discussion in memorandum from Hugh McKinnon, EPA, to Michael Callahan, EPA, November 9, 1990).

6. ASSESSING UNCERTAINTY

Assessing uncertainty may involve simple or very sophisticated techniques, depending on the requirements of the assessment. Uncertainty *characterization* and uncertainty *assessment* are two activities that lead to different degrees of sophistication in describing uncertainty. Uncertainty characterization generally involves a qualitative discussion of the thought processes that lead to the selection and rejection of specific data, estimates, scenarios, etc. For simple exposure assessments, where not much quantitative information is available, uncertainty characterization may be all that is necessary.

The uncertainty assessment is more quantitative. The process begins with simpler measures (i.e., ranges) and simpler analytical techniques (i.e., sensitivity analysis), and progresses, to the extent needed to support the decision for which the exposure assessment is conducted, to more complex measures and techniques. The development and implementation of an appropriate uncertainty assessment strategy can be viewed as a decision process. Decisions are made about ways to characterize and analyze uncertainties, and whether to proceed to increasingly more complex levels of uncertainty assessment.

6.1. ROLE OF UNCERTAINTY ANALYSIS IN EXPOSURE ASSESSMENT

Exposure assessment uses a wide array of information sources and techniques. Even where actual exposure-related measurements exist, assumptions or inferences will still be required (see Section 5.2). Most likely, data will not be available for all aspects of the exposure assessment and those data that are available may be of questionable or unknown quality. In these situations, the exposure assessor will have to rely on a combination of professional judgment, inferences based on analogy with similar chemicals and conditions, estimation techniques, and the like. The net result is that the exposure assessment will be based on a number of assumptions with varying degrees of uncertainty.

The decision analysis literature has focused on the importance of explicitly incorporating and quantifying scientific uncertainty in risk assessments (Morgan, 1983; Finkel, 1990). Reasons for addressing uncertainties in exposure assessments include:

- Uncertain information from different sources of different quality must be combined.
- A decision must be made about whether and how to expend resources to acquire additional information (e.g., production, use, and emissions data; environmental fate information; monitoring data; population data) to reduce the uncertainty.
- There is considerable empirical evidence that biases may result in so-called best estimates that are not actually very accurate. Even if all that is needed is a best-

estimate answer, the quality of that answer may be improved by an analysis that incorporates a frank discussion of uncertainty.

- Exposure assessment is an iterative process. The search for an adequate and robust methodology to handle the problem at hand may proceed more effectively, and to a more certain conclusion, if the associated uncertainty is explicitly included and can be used as a guide in the process of refinement.
- A decision is rarely made on the basis of a single piece of analysis. Further, it is rare for there to be one discrete decision; a process of multiple decisions spread over time is the more common occurrence. Chemicals of concern may go through several levels of risk assessment before a final decision is made. Within this process, decisions may be made based on exposure considerations. An exposure analysis that attempts to characterize the associated uncertainty allows the user or decision-maker to better evaluate it in the context of the other factors being considered.
- Exposure assessors have a responsibility to present not just numbers but also a clear and explicit explanation of the implications and limitations of their analyses. Uncertainty characterization helps carry out this responsibility.

Essentially, the construction of scientifically sound exposure assessments and the analysis of uncertainty go hand in hand. The reward for analyzing uncertainties is knowing that the results have integrity or that significant gaps exist in available information that can make decision-making a tenuous process.

6.2. TYPES OF UNCERTAINTY

Uncertainty in exposure assessment can be classified into three broad categories:

1. Uncertainty regarding missing or incomplete information needed to fully define the exposure and dose (scenario uncertainty)
2. Uncertainty regarding some parameter (parameter uncertainty)
3. Uncertainty regarding gaps in scientific theory required to make predictions on the basis of causal inferences (model uncertainty)

Identification of the sources of uncertainty in an exposure assessment is the first step toward eventually determining the type of action necessary to reduce that uncertainty. The three types of uncertainty mentioned above can be further defined by examining some principal causes for each.

Exposure assessments often are developed in a phased approach. The initial phase usually involves some type of broad-based screening in which the scenarios that are not expected to pose a risk to the receptor are eliminated from a more detailed, resource-intensive review, usually through developing bounding estimates. These screening-level scenarios often are

constructed to represent exposures that would fall beyond the extreme upper end of the expected exposure distribution. Because the screening-level assessments for these nonproblem scenarios usually are included in the final exposure assessment document, this final document may contain scenarios that differ quite markedly in level of sophistication, quality of data, and amenability to quantitative expressions of uncertainty. These also can apply to the input parameters used to construct detailed exposure scenarios.

The following sections will discuss sources, characterization, and methods for analyzing the different types of uncertainty.

6.2.1. Scenario Uncertainty

The sources of scenario uncertainty include descriptive errors, aggregation errors, errors in professional judgment, and incomplete analysis.

Descriptive errors include errors in information, such as the current producers of the chemical and its industrial, commercial, and consumer uses. Information of this type is the foundation for the eventual development of exposure pathways, scenarios, exposed populations, and exposure estimates.

Aggregation errors arise as a result of lumping approximations. Included among these are assumptions of homogeneous populations, and spatial and temporal approximations such as assumptions of steady-state conditions.

Professional judgment comes into play in virtually every aspect of the exposure assessment process, from defining the appropriate exposure scenarios, to selecting the proper environmental fate models, to determining representative environmental conditions, etc. Errors in professional judgment also are a source of uncertainty.

A potentially serious source of uncertainty in exposure assessments arises from incomplete analysis. For example, the exposure assessor may overlook an important consumer exposure due to lack of information regarding the use of a chemical in a particular product. Although this source of uncertainty is essentially unquantifiable, it should not be overlooked by the assessor. At a minimum, the rationale for excluding particular exposure scenarios should be described and the uncertainty in those decisions should be characterized as high, medium, or low. The exposure assessor should discuss whether these decisions were based on actual data, analogues, or professional judgment. For situations in which the uncertainty is high, one should perform a reality check where credible upper limits on the exposure are established by a "what if" analysis.

Characterization of the uncertainty associated with nonnumeric assumptions (often relating to setting the assessment's direction and scope) will generally involve a qualitative discussion of the rationale used in selecting specific scenarios. The discussion should allow the

reader to make an independent judgment about the validity of the conclusions reached by the assessor by describing the uncertainty associated with any inferences, extrapolations, and analogies used and the weight of evidence that led the assessor to particular conclusions.

6.2.2. Parameter Uncertainty

Sources of parameter uncertainty include measurement errors, sampling errors, variability, and use of generic or surrogate data.

Measurement errors can be random or systematic. Random error results from imprecision in the measurement process. Systematic error is a bias or tendency away from the true value.

Sampling errors concern sample representativeness. The purpose of sampling is to make an inference about the nature of the whole from a measurement of a subset of the total population. If the exposure assessment uses data that were generated for another purpose, for example, consumer product preference surveys or compliance monitoring surveys, uncertainty will arise if the data do not represent the exposure scenario being analyzed.

The inability to characterize the inherent variability in environmental and exposure-related parameters is a major source of uncertainty. For example, meteorological and hydrological conditions may vary seasonally at a given location, soil conditions can have large spatial variability, and human activity patterns can vary substantially depending on age, sex, and geographical location.

The use of generic or surrogate data is common when site-specific data are not available. Examples include standard emission factors for industrial processes, generalized descriptions of environmental settings, and data pertaining to structurally related chemicals as surrogates for the chemical of interest. This is an additional source of uncertainty, and should be avoided if actual data can be obtained.

The approach to characterizing uncertainty in parameter values will vary. It can involve an order-of-magnitude bounding of the parameter range when uncertainty is high, or a description of the range for each of the parameters including the lower- and upper-bound and the best estimate values and justification for these based on available data or professional judgment. In some circumstances, characterization can take the form of a probabilistic description of the parameter range. The appropriate characterization will depend on several factors, including whether a sensitivity analysis indicates that the results are significantly affected by variations within the range. When the results are significantly affected by a particular parameter, the exposure assessor should attempt to reduce the uncertainty by developing a description of the likely occurrence of particular values within the range. If enough data are available, standard statistical methods can be used to obtain a meaningful representation. If available data are

inadequate, then expert judgments can be used to develop a subjective probabilistic representation. Expert judgments should be developed in a consistent, well-documented manner. Examples of techniques to solicit expert judgments have been described (Morgan et al., 1979; Morgan et al., 1984; Rish, 1988).

Most approaches for analyzing uncertainty have focused on techniques that examine how uncertainty in parameter values translates into overall uncertainty in the assessment. Several published reports (Cox and Baybutt, 1981; U.S. EPA, 1985f; Inman and Helton, 1988; Seller, 1987; Rish and Marnicio, 1988) have reviewed the many techniques available; the assessor should consult these for details. In general, these approaches can be described, in order of increasing complexity and data requirements, as either sensitivity analysis, analytical uncertainty propagation, probabilistic uncertainty analysis, or classical statistical methods.

Sensitivity analysis is the process of changing one variable while leaving the others constant and determining the effect on the output. The procedure involves fixing each uncertain quantity, one at a time, at its credible lower-bound and then its upper-bound (holding all others at their medians), and then computing the outcomes for each combination of values. These results are useful to identify the variables that have the greatest effect on exposure and to help focus further information gathering. The results do not provide any information about the probability of a quantity's value being at any level within the range; therefore, this approach is most useful at the screening level when deciding about the need and direction of further analyses.

Analytical uncertainty propagation involves examining how uncertainty in individual parameters affects the overall uncertainty of the exposure assessment. Intuitively, it seems clear that uncertainty in a specific parameter may propagate very differently through a model than another variable having approximately the same uncertainty. Some parameters are more important than others, and the model structure is designed to account for the relative sensitivity. Thus, uncertainty propagation is a function of both the data and the model structure. Accordingly, both model sensitivity and input variances are evaluated in this procedure. Application of this approach to exposure assessment requires explicit mathematical expressions of exposure, estimates of the variances for each of the variables of interest, and the ability either analytically or numerically to obtain a mathematical derivative of the exposure equation.

Although uncertainty propagation is a powerful tool, it should be applied with caution, and the assessor should consider several points. It is difficult to generate and solve the equations for the sensitivity coefficients. In addition, the technique is most accurate for linear equations, so any departure from linearity must be carefully evaluated. Assumptions, such as independence of variables and normality of errors in the variables, need to be checked. Finally, this approach

requires estimates of parameter variance, and the information to support these may not be readily available.

Probabilistic uncertainty analysis is generally considered the next level of refinement. The most common example is the Monte Carlo technique where probability density functions are assigned to each parameter, then values from these distributions are randomly selected and inserted into the exposure equation. After this process is completed many times, a distribution of predicted values results that reflects the overall uncertainty in the inputs to the calculation.

The principal advantage of the Monte Carlo method is its very general applicability. There is no restriction on the form of the input distributions or the nature of the relationship between input and output; computations are also straightforward. There are some disadvantages as well as inconveniences, however. The exposure assessor should only consider using this technique when there are credible distribution data (or ranges) for most key variables. Even if these distributions are known, it may not be necessary to apply this technique. For example, if only average exposure values are needed, these can often be computed as accurately by using average values for each of the input parameters. Another inconvenience is that the sensitivity of the results to the input distributions is somewhat cumbersome to assess. Changing the distribution of only one value requires rerunning the entire calculation (typically, several hundreds or thousands of times). Finally, Monte Carlo results do not tell the assessor which variables are the most important contributors to output uncertainty. This is a disadvantage since most analyses of uncertainty are performed to find effective ways to reduce uncertainty.

Classical statistical methods can be used to analyze uncertainty in measured exposures. Given a data set of measured exposure values for a series of individuals, the population distribution may be estimated directly, provided that the sample design was developed properly to capture a representative sample. The measured exposure values also may be used to directly compute confidence interval estimates for percentiles of the exposure distribution (American Chemical Society, 1988). When the exposure distribution is estimated from measured exposures for a probability sample of population members, confidence interval estimates for percentiles of the exposure distribution are the primary uncertainty characterization. Data collection survey design should also be discussed, as well as accuracy and precision of the measurement techniques.

Often the observed exposure distribution is skewed; many sample members have exposure distributions at or below the detection limit. In this situation, estimates of the exposure distribution may require a very large sample size. Fitting the data to a distribution type can be problematic in this situation because data are usually scant in the low probability areas (the tails) where numerical values vary widely. As a consequence, for data sets for which the sampling has been completed, means and standard deviations may be determined to a good approximation, but

characterization of the tails of the distribution will have much greater uncertainty. This difference should be brought out in the discussion. For data sets for which sampling is still practical, stratification of the statistical population to oversample the tail may give more precision and confidence in the information in the tail area of the distribution.

6.2.3. Model Uncertainty

At a minimum, the exposure assessor should describe in qualitative terms the rationale for selection of any conceptual and mathematical models. This discussion should address the status of these approaches and any plausible alternatives in terms of their acceptance by the scientific community, how well the model(s) represents the situation being assessed, e.g., high-end estimate, and to what extent verification and validation have been done. Relationship errors and modeling errors are the primary sources of modeling uncertainty.

Relationship errors include errors in correlations between chemical properties, structure-reactivity correlations, and environmental fate models. In choosing to use these tools, the exposure assessor must decide among the many possible functional forms available. Even though statistics on the performance of the methodology for a given test set of chemicals may be available and can help guide in the selection process, the exposure assessor must decide on the most appropriate methodology for the chemical of interest based on the goals of the assessment.

Modeling errors are due to models being simplified representations of reality, for example approximating a three-dimensional aquifer with a two-dimensional mathematical model. Even after the exposure assessor has selected the most appropriate model for the purpose at hand, one is still faced with the question of how well the model represents the real situation. This question is compounded by the overlap between modeling uncertainties and other uncertainties, e.g., natural variability in environmental inputs, representativeness of the modeling scenario, and aggregation errors. The dilemma facing exposure assessors is that many existing models (particularly the very complex ones) and the hypotheses contained within them cannot be fully tested (Beck, 1987), although certain components of the model may be tested. Even when a model has been validated under a particular set of conditions, uncertainty will exist in its application to situations beyond the test system.

A variety of approaches can be used to quantitatively characterize the uncertainty associated with model constructs. One approach is to use different modeling formulations (including the preferred and plausible alternatives) and consider the range of the outputs to be representative of the uncertainty range. This strategy is most useful when no clear best approach can be identified due to the lack of supporting data or when the situations being assessed require extrapolation beyond the conditions for which the models were originally designed.

Where the data base is sufficient, the exposure assessor should characterize the uncertainty in the selected model by describing the validation and verification efforts. Validation is the process of examining the performance of the model compared to actual observations under situations representative of those being assessed. Approaches for model validation have been discussed (U.S. EPA 1985e). Verification is the process of confirming that the model computer code is producing the proper numerical output. In most situations, only partial validation is possible due to data deficiencies or model complexity.

6.3. VARIABILITY WITHIN A POPULATION VERSUS UNCERTAINTY IN THE ESTIMATE

For clarity, it should be emphasized that variability (the receipt of different levels of exposure by different individuals) is being distinguished from uncertainty (the lack of knowledge about the correct value for a specific exposure measure or estimate). Most of the exposure and risk descriptors discussed in this report deal with variability directly, but estimates must also be made of the uncertainty of these descriptors.[42] This may be done qualitatively or quantitatively, and it is beyond the scope of this report to discuss the mechanics of uncertainty analysis in detail. It is an important distinction, however, since the risk assessor and risk manager need to know if the numbers being reported for exposures take variability, uncertainty, or both, into consideration.

Not all approaches historically used to construct measures or estimates of exposure attempted to distinguish variability and uncertainty. In particular, in many cases in which estimates were termed worst case, focusing on the high end of the exposed population and also selection of high-end values for uncertain physical quantities resulted in values that were seen to be quite conservative. By using both the high-end individuals (variability) and upper confidence bounds[43] on data or physical parameters (uncertainty), these estimates might be interpreted as "not exceeding an upper bound on exposures received by certain high-end individuals."

Note that this approach will provide an estimate that considers both variability and uncertainty, but by only reporting the upper confidence bound, it appears to be merely a more

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[42]Each measure or estimate of exposure will have its associated uncertainty which should be addressed both qualitatively and quantitatively. For example, if population mean exposure is being addressed by use of direct personal monitoring data, qualitative issues will include the representativeness of the population monitored to the full population, the representativeness of the period selected for monitoring, and confidence that there were not systematic errors in the measured data. Quantitative uncertainty could be addressed through the use of confidence intervals for the actual mean population exposure.

[43]The confidence interval is interpreted as the range of values within which the assessor knows the true measure lies, with specified statistical confidence. The upper bound confidence limit is the higher of the two ends of the confidence interval.

conservative estimate of the variability. High-end estimates which include consideration of uncertainty should be presented with both the upper and lower uncertainty bounds on the high-end estimate. This provides the necessary information to the risk manager. Without specific discussion of what was done, risk managers may view the results as not having dealt with uncertainty. It is fundamental to exposure assessment that assessors have a clear distinction between the variability of exposures received by individuals in a population, and the uncertainty of the data and physical parameters used in calculating exposure.

The discussion of estimating exposure and dose presented in Section 5.3.4 addresses the rationale and approaches for constructing a range of measures or estimates of exposure, with emphasis on how these can be used for exposure or risk characterization. The distinction between these measures or estimates (e.g., average versus high end) is often a difference in anticipated variability in the exposures received by individuals (i.e., average exposure integrates exposures across all individuals, while high-end exposure focuses on the upper percentiles of the exposed group being assessed.) Although several measures can be used to characterize risk in different ways, this does not address which of these measures or characterizations is used for decisions. The selection of the point or measure of exposure or risk upon which regulatory decisions are made is a risk management decision governed by programmatic policy, and is therefore beyond the scope of these guidelines.

7. PRESENTING THE RESULTS OF THE EXPOSURE ASSESSMENT

One of the most important aspects of the exposure assessment is presenting the results. It is here that the assessment ultimately succeeds or fails in meeting the objectives laid out in the planning as discussed in Section 3. This section discusses communication of the results, format considerations, and suggested tips for reviewing exposure assessments either as a final check or as a review of work done by others.

7.1. COMMUNICATING THE RESULTS OF THE ASSESSMENT

Communicating the results of an exposure assessment is more than a simple summary of conclusions and quantitative estimates for the various pathways and routes of exposure. The most important part of an exposure assessment is the overall narrative exposure characterization, without which the assessment is merely a collection of data, calculations, and estimates. This exposure characterization should consist of discussion, analysis, and conclusions that synthesize the results from the earlier portions of the document, present a balanced representation of the available data and its relevancy to the health effects of concern, and identify key assumptions and major areas of uncertainty. Section 7.1.1 discusses the exposure characterization, and Section 7.1.2 discusses how this is used in the risk characterization step of a risk assessment.

7.1.1. Exposure Characterization

The exposure characterization is the summary explanation of the exposure assessment. In this final step, the exposure characterization:

- provides a statement of purpose, scope, level of detail, and approach used in the assessment, including key assumptions;
- presents the estimates of exposure and dose by pathway and route for individuals, population segments, and populations in a manner appropriate for the intended risk characterization;
- provides an evaluation of the overall quality of the assessment and the degree of confidence the authors have in the estimates of exposure and dose and the conclusions drawn;
- interprets the data and results; and
- communicates results of the exposure assessment to the risk assessor, who can then use the exposure characterization, along with characterizations of the other risk assessment elements, to develop a risk characterization.

As part of the statement of purpose, the exposure characterization explains why the assessment was done and what questions were asked. It also reaches a conclusion as to whether

the questions posed were in fact answered, and with what degree of confidence. It should also note whether the exposure assessment brought to light additional or perhaps more appropriate questions, if these were answered, and if so, with what degree of confidence.

The statement of scope discusses the geographical or demographic boundaries of the assessment. The specific populations and population segments that were the subjects of the assessment are clearly identified, and the reasons for their selection and any exclusions are discussed. Especially sensitive groups or groups that may experience unusual exposure patterns are highlighted.

The characterization also discusses whether the scope and level of detail of the assessment were ideal for answering the questions of the assessment and whether limitations in scope and level of detail were made because of technical, practical, or financial reasons, and the implications of these limitations on the quality of the conclusions.

The methods used to quantify exposure and dose are clearly stated in the exposure characterization. If models are used, the basis for their selection and validation status is described. If measurement data are used, the quality of the data is discussed. The strengths and weaknesses of the particular methods used to quantify exposure and dose are described, along with comparison and contrast to alternate methods, if appropriate.

In presenting the exposure and dose estimates, the important sources, pathways, and routes of exposure are identified and quantified, and reasons for excluding any from the assessment are discussed.

A variety of risk descriptors, and where possible, the full population distribution is presented. Risk managers should be given some sense of how exposure is distributed over the population and how variability in population activities influences this distribution. Ideally, the exposure characterization links the purpose of the assessment with specific risk descriptors, which in turn are presented in such a way as to facilitate construction of a risk characterization.

A discussion of the quality of the exposure and dose estimates is critical to the credibility of the assessment. This may be based in part on a quantitative uncertainty analysis, but the exposure characterization must explain the results of any such analysis in terms of the degree of confidence to be placed in the estimates and conclusions drawn.

Finally, a description of additional research and data needed to improve the exposure assessment is often helpful to risk managers in making decisions about improving the quality of the assessment. For this reason, the exposure characterization should identify key data gaps that can help focus further efforts to reduce uncertainty.

Additional guidance on communicating the results of an exposure assessment can be found in the proceedings of a recent workshop on risk communication (American Industrial Health Council, 1989).

7.1.2. Risk Characterization

Most exposure assessments will be done as part of a risk assessment, and the exposure characterization must be useful to the risk assessor in constructing a risk characterization. Risk characterization is the integration of information from hazard identification, dose-response assessment, and exposure assessment into a coherent picture. A risk characterization is a necessary part of any Agency report on risk whether the report is a preliminary one prepared to support allocation of resources toward further study or a comprehensive one prepared to support regulatory decisions.

Risk characterization is the culmination of the risk assessment process. In this final step, the risk characterization:

- integrates the individual characterizations from the hazard identification, dose-response, and exposure assessments;
- provides an evaluation of the overall quality of the assessment and the degree of confidence the authors have in the estimates of risk and conclusions drawn;
- describes risks to individuals and populations in terms of extent and severity of probable harm; and
- communicates results of the risk assessment to the risk manager.

It provides a scientific interpretation of the assessment. The risk manager can then use the risk assessment, along with other risk management elements, to make public health decisions. The following sections describe these four aspects of the risk characterization in more detail.

7.1.2.1. *Integration of Hazard Identification, Dose-Response, and Exposure Assessments*

In developing the hazard identification, dose-response, and exposure portions of the risk assessment, the assessor makes many judgments concerning the relevance and appropriateness of data and methodology. These judgments are summarized in the individual characterizations for hazard identification, dose-response, and exposure. In integrating the parts of the assessment, the risk assessor determines if some of these judgments have implications for other parts of the assessment, and whether the parts of the assessment are compatible. For example, if the hazard identification assessment determines that a chemical is a developmental toxicant but not a carcinogen, the dose-response and exposure information is presented accordingly; this differs greatly from the way the presentation is made if the chemical is a carcinogen but not a developmental toxicant.

The risk characterization not only examines these judgments, but also explains the constraints of available data and the state of knowledge about the phenomena studied in making them, including:

- the qualitative, weight-of-evidence conclusions about the likelihood that the chemical may pose a specific hazard (or hazards) to human health, the nature and severity of the observed effects, and by what route(s) these effects are seen to occur. These judgments affect both the dose-response and exposure assessments;
- for noncancer effects, a discussion of the dose-response behavior of the critical effect(s), data such as the shapes and slopes of the dose-response curves for the various other toxic endpoints, and how this information was used to determine the appropriate dose-response assessment technique; and
- the estimates of the magnitude of the exposure, the route, duration and pattern of the exposure, relevant pharmacokinetics, and the number and characteristics of the population exposed. This information must be compatible with both the hazard identification and dose-response assessments.

The presentation of the integrated results of the assessment draws from and highlights key points of the individual characterizations of hazard, dose-response, and exposure analysis performed separately under these Guidelines. The summary integrates these component characterizations into an overall risk characterization.

7.1.2.2. *Quality of the Assessment and Degree of Confidence*

The risk characterization summarizes the data brought together in the analysis and the reasoning upon which the assessment is based. The description also conveys the major strengths and weaknesses of the assessment that arise from data availability and the current limits of understanding of toxicity mechanisms.

Confidence in the results of a risk assessment is consequently a function of confidence in the results of analysis of each element: hazard, dose-response, and exposure. Each of these three elements has its own characterization associated with it. For example, the exposure assessment component includes an exposure characterization. Within each characterization, the important uncertainties of the analysis and interpretation of data are explained so that the risk manager is given a clear picture of any consensus or lack thereof about significant aspects of the assessment. For example, whenever more than one view of dose-response assessment is supported by the data and by the policies of these Guidelines, and choosing between them is difficult, the views are presented together. If one has been selected over another, the rationale is given; if not, then both are presented as plausible alternatives.

If a quantitative uncertainty analysis is appropriate, it is summarized in the risk characterization; in any case a qualitative discussion of important uncertainties is appropriate. If other organizations, such as other Federal agencies, have published risk assessments, or prior

EPA assessments have been done on the substance or an analogous substance and have relevant similarities or differences, these too are described.

7.1.2.3. *Descriptors of Risk*

There are a number of different ways to describe risk in quantitative or qualitative terms. Section 2.3 explains how risk descriptors are used. It is important to explain what aspect of the risk is being described, and how the exposure data and estimates are used to develop the particular descriptor.

7.1.2.4. *Communicating Results of a Risk Assessment to the Risk Manager*

Once the risk characterization is completed, the focus turns to communicating results to the risk manager. The risk manager uses the results of the risk characterization, technologic factors, and socioeconomic considerations in reaching a regulatory decision. Because of the way these risk management factors may impact different cases, consistent, but not necessarily identical, risk management decisions must be made on a case-by-case basis. Consequently, it is entirely possible and appropriate that a chemical with a specific risk characterization may be regulated differently under different statutes. These Guidelines are not intended to give guidance on the nonscientific aspects of risk management decisions.

7.1.3. Establishing the Communication Strategy

For assessments that must be explained to the general public, a communication strategy is often required. Although risk communication is often considered a part of risk management, it involves input from the exposure and risk assessors; early planning for a communication strategy can be very helpful to the ultimate risk communication.

The EPA has guidance on preparing communication strategies (U.S. EPA, 1988g). Additional sources of information are the New Jersey Department of Environmental Protection (1988a, 1988b) and the NRC (1989b). These documents, and the sources listed within them, are valuable resources for all who will be involved with the sensitive issues of explaining environmental health risks. The NRC (1989b, p. 148) states:

> It is a mistake to simply consider risk communication to be an add-on activity for either scientific or public affairs staffs; both elements should be involved. There are clear dangers if risk messages are formulated *ad hoc* by public relations personnel in isolation from available technical expertise; neither can they be prepared by risk analysts as a casual extension of their analytic duties.

7.2. FORMAT FOR EXPOSURE ASSESSMENT REPORTS

The Agency does not require a set format for exposure assessment reports, but individual program offices within the Agency may have specific format requirements. Section 3 illustrates that exposure assessments are performed for a variety of purposes, scopes, and levels of detail, and use a variety of approaches. While it is impracticable for the Agency to specify an outline format for all types of assessments being performed within the Agency, program offices are encouraged to use consistent formats for similar types of assessments within their own purview.

All exposure assessments must, at a minimum, contain a narrative exposure characterization section that contains the types of information discussed in Section 7.1. For the purpose of consistency, this section should be titled exposure characterization. Placement of this section within the assessment is optional, but it is strongly suggested that it be prominently featured in the assessment. It is not, however, an executive summary and should not be used interchangeably with one.

7.3. REVIEWING EXPOSURE ASSESSMENTS

This section provides some suggestions on how to effectively review an exposure assessment and highlights some of the common pitfalls. The emphasis in these Guidelines has been on how to properly conduct exposure assessments; this section can serve as a final checklist in reviewing the completed assessment. An exposure assessor also may be called upon to critically review and evaluate exposure assessments conducted by others; these suggestions should be helpful in this regard.

Reviewers of exposure assessments are usually asked to identify inconsistences with the underlying science and with Agency-developed guidelines, factors, and methodologies, and to determine the effect these inconsistences might have on the results and conclusions of the exposure assessment. Often the reviewer can only describe whether these inconsistencies or deficiencies might underestimate or overestimate exposure.

Some of the questions a reviewer should ask to identify the more common pitfalls that tend to underestimate exposure are:

Has the pathways analysis been broad enough to avoid overlooking a significant pathway? For example, in evaluating exposure to soil contaminated with PCBs, the exposure assessment should not be limited only to evaluating the dermal contact pathway. Other pathways, such as inhalation of dust and vapors or the ingestion of contaminated gamefish from an adjacent stream receiving surface runoff containing contaminated soil, should also be evaluated as they could contribute higher levels of exposure from the same source.

Have all the contaminants of concern in a mixture been evaluated? Since risks resulting from exposures to complex mixtures of chemicals with the same mode of toxic action are

generally treated as additive (by summing the risks) in a risk assessment, failure to evaluate one or more of the constituents would neglect its contribution to the total exposure and risk. This is especially critical for relatively toxic or potent chemicals that tend to drive risk estimates even when present in relatively low quantities.

Have exposure levels or concentration measurements been compared with appropriate background levels? Contaminant concentrations or exposure levels should not be compared with other contaminated media or exposed populations. When comparing with background levels, the exposure assessor must determine whether these concentrations or exposure levels are also affected by contamination from anthropogenic activities.

Were the detection limits sensitive enough to make interpretations about exposures at levels corresponding to health concerns? Were the data interpreted correctly? Because values reported as not detected (ND) mean only that the chemical of interest was not found at the particular detection limit used in the laboratory analysis, ND does not rule out the possibility that the chemical may be present in significant concentrations. Depending on the purpose and the degree of conservatism warranted in the exposure assessment, results reported as ND should be handled as discussed in Section 5.

Has the possibility of additive pathways been considered for the population being studied? If the purpose of the exposure assessment is to evaluate the total exposure and risk of a population, then exposures from individual pathways within the same route may be summed in cases which concurrent exposures can *realistically* be expected to occur.

Some questions a reviewer should ask to avoid the more prevalent errors that generally tend to overestimate exposure are:

Have unrealistically conservative exposure parameters been used in the scenarios? The exposure assessor must conduct a reality check to ensure that the exposure cases used in the scenario(s) (except bounding estimates) could actually occur.

Have potential exposures been presented as existing exposures? In many situations, especially when the scenario evaluation approach is used, the objective of the assessment is to estimate potential exposures. (That is, *if* a person were to be exposed to these chemicals under these conditions, then the resultant exposure would be this much.) In determining the need and urgency for regulatory action, risk managers often weigh actual exposures more heavily than higher levels of potential exposures. Therefore, the exposure assessment should clearly note whether the results represent actual or potential exposures.

Have exposures derived from "not detected" levels been presented as actual exposures? For some exposure assessments it may be appropriate to assume that a chemical reported as not detected is present at either the detection limit or one-half the detection limit. The exposure estimates derived from these nondetects, however, should be clearly labeled as hypothetical

since they are based on the conservative assumption that chemicals are present at or below the detection limit, when, in fact, they may not be present at all. Exposures, doses, or risks estimated from data using substituting values of detection limits for "not detected" samples must be reported as "less than" the resulting exposure, dose, or risk estimate.

Questions a reviewer should ask to identify common errors that may underestimate or overestimate exposure are:

Are the results presented with an appropriate number of significant figures? The number of significant figures should reflect the uncertainty of the numeric estimate. If the likely range of the results spans several orders of magnitude, then using more than one significant figure implies more confidence in the results than is warranted.

Have the calculations been checked for computational errors? Obviously, calculations should be checked for arithmetic errors and mistakes in converting units. This is overlooked more often than one might expect.

Are the factors for intake rates, etc. used appropriately? Exposure factors should be checked to ensure that they correspond to the site or situation being evaluated.

Have the uncertainties been adequately addressed? Exposure assessment is an inexact science, and the confidence in the results may vary tremendously. It is essential the exposure assessment include an uncertainty assessment that places these uncertainties in perspective.

If Monte Carlo simulations were used, were correlations among input distributions known and properly accounted for? Is the maximum value simulated by this method in fact a bounding estimate? Was Monte Carlo simulation necessary? (A Monte Carlo simulation randomly selects the values from the input parameters to simulate an individual. If data already exist to show the relationship between variables for the actual individuals, it makes little sense to use Monte Carlo simulation, since one already has the answer to the question of how the variables are related for each individual. A simulation is unnecessary.)

8. GLOSSARY OF TERMS

Absorbed dose - See internal dose.

Absorption barrier - Any of the exchange barriers of the body that allow differential diffusion of various substances across a boundary. Examples of absorption barriers are the skin, lung tissue, and gastrointestinal tract wall.

Accuracy - The measure of the correctness of data, as given by the difference between the measured value and the true or standard value.

Administered dose - The amount of a substance given to a test subject (human or animal) in determining dose-response relationships, especially through ingestion or inhalation. In exposure assessment, since exposure to chemicals is usually inadvertent, this quantity is called potential dose.

Agent - A chemical, physical, mineralogical, or biological entity that may cause deleterious effects in an organism after the organism is exposed to it.

Ambient - The conditions surrounding a person, sampling location, etc.

Ambient measurement - A measurement (usually of the concentration of a chemical or pollutant) taken in an ambient medium, normally with the intent of relating the measured value to the exposure of an organism that contacts that medium.

Ambient medium - One of the basic categories of material surrounding or contacting an organism, e.g., outdoor air, indoor air, water, or soil, through which chemicals or pollutants can move and reach the organism. (See also biological medium, environmental medium)

Applied dose - The amount of a substance in contact with the primary absorption boundaries of an organism (e.g., skin, lung, gastrointestinal tract) and available for absorption.

Arithmetic mean - The sum of all the measurements in a data set divided by the number of measurements in the data set.

Background level (environmental) - The concentration of substance in a defined control area during a fixed period of time before, during, or after a data-gathering operation.

Breathing zone - A zone of air in the vicinity of an organism from which respired air is drawn. Personal monitors are often used to measure pollutants in the breathing zone.

Bias - A systematic error inherent in a method or caused by some feature of the measurement system.

Bioavailability - The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Bioavailability is typically a function of chemical

properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical.

Biological marker of exposure (sometimes referred to as a biomarker of exposure) - Exogenous chemicals, their metabolites, or products of interactions between a xenobiotic chemical and some target molecule or cell that is measured in a compartment within an organism.

Biological measurement - A measurement taken in a biological medium. For the purpose of exposure assessment via reconstruction of dose, the measurement is usually of the concentration of a chemical/metabolite or the status of a biomarker, normally with the intent of relating the measured value to the internal dose of a chemical at some time in the past. (Biological measurements are also taken for purposes of monitoring health status and predicting effects of exposure.) (See also ambient measurement)

Biological medium - One of the major categories of material within an organism, e.g., blood, adipose tissue, or breath, through which chemicals can move, be stored, or be biologically, physically, or chemically transformed. (See also ambient medium, environmental medium)

Biologically effective dose - The amount of a deposited or absorbed chemical that reaches the cells or target site where an adverse effect occurs, or where that chemical interacts with a membrane surface.

Blank (blank sample) - An unexposed sampling medium, or an aliquot of the reagents used in an analytical procedure, in the absence of added analyte. The measured value of a blank sample is the blank value.

Body burden - The amount of a particular chemical stored in the body at a particular time, especially a potentially toxic chemical in the body as a result of exposure. Body burdens can be the result of long-term or short-term storage, for example, the amount of a metal in bone, the amount of a lipophilic substance such as PCB in adipose tissue, or the amount of carbon monoxide (as carboxyhemoglobin) in the blood.

Bounding estimate - An estimate of exposure, dose, or risk that is higher than that incurred by the person in the population with the highest exposure, dose, or risk. Bounding estimates are useful in developing statements that exposures, doses, or risks are "not greater than" the estimated value.

Comparability - The ability to describe likenesses and differences in the quality and relevance of two or more data sets.

Data quality objectives (DQO) - Qualitative and quantitative statements of the overall level of uncertainty that a decision-maker is willing to accept in results or decisions derived from environmental data. DQOs provide the statistical framework for planning and managing environmental data operations consistent with the data user's needs.

Dose - The amount of a substance available for interaction with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The potential dose is the amount ingested, inhaled, or applied to the skin. The applied dose is the amount of a substance presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The absorbed dose is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of skin, lung, and digestive tract) through uptake processes. Internal dose is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction by any particular organ or cell is termed the delivered dose for that organ or cell.

Dose rate - Dose per unit time, for example in mg/day, sometimes also called dosage. Dose rates are often expressed on a per-unit-body-weight basis, yielding units such as mg/kg/day (mg/kg-day). They are also often expressed as averages over some time period, for example a lifetime.

Dose-response assessment - The determination of the relationship between the magnitude of administered, applied, or internal dose and a specific biological response. Response can be expressed as measured or observed incidence, percent response in groups of subjects (or populations), or the probability of occurrence of a response in a population.

Dose-response curve - A graphical representation of the quantitative relationship between administered, applied, or internal dose of a chemical or agent, and a specific biological response to that chemical or agent.

Dose-response relationship - The resulting biological responses in an organ or organism expressed as a function of a series of different doses.

Dosimeter - Instrument to measure dose; many so-called dosimeters actually measure exposure rather than dose.

Dosimetry - Process of measuring or estimating dose.

Ecological exposure - Exposure of a nonhuman receptor or organism to a chemical, or a radiological or biological agent.

Effluent - Waste material being discharged into the environment, either treated or untreated. Effluent generally is used to describe water discharges to the environment, although it can refer to stack emissions or other material flowing into the environment.

Environmental fate - The destiny of a chemical or biological pollutant after release into the environment. Environmental fate involves temporal and spatial considerations of transport, transfer, storage, and transformation.

Environmental fate model - In the context of exposure assessment, any mathematical abstraction of a physical system used to predict the concentration of specific chemicals as a

function of space and time subject to transport, intermedia transfer, storage, and degradation in the environment.

Environmental medium - One of the major categories of material found in the physical environment that surrounds or contacts organisms, e.g., surface water, ground water, soil, or air, and through which chemicals or pollutants can move and reach the organisms. (See ambient medium, biological medium)

Exposure - Contact of a chemical, physical, or biological agent with the outer boundary of an organism. Exposure is quantified as the concentration of the agent in the medium in contact integrated over the time duration of that contact.

Exposure assessment - The determination or estimation (qualitative or quantitative) of the magnitude, frequency, duration, and route of exposure.

Exposure concentration - The concentration of a chemical in its transport or carrier medium at the point of contact.

Exposure pathway - The physical course a chemical or pollutant takes from the source to the organism exposed.

Exposure route - The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.

Exposure scenario - A set of facts, assumptions, and inferences about how exposure takes place that aids the exposure assessor in evaluating, estimating, or quantifying exposures.

Fixed-location monitoring - Sampling of an environmental or ambient medium for pollutant concentration at one location continuously or repeatedly over some length of time.

Geometric mean - The n^{th} root of the product of n values.

Guidelines - Principles and procedures to set basic requirements for general limits of acceptability for assessments.

Hazard identification - A description of the potential health effects attributable to a specific chemical or physical agent. For carcinogen assessments, the hazard identification phase of a risk assessment is also used to determine whether a particular agent or chemical is, or is not, causally linked to cancer in humans.

High-end exposure (dose) estimate - A plausible estimate of individual exposure or dose for those persons at the upper end of an exposure or dose distribution, conceptually above the 90^{th} percentile, but not higher than the individual in the population who has the highest exposure or dose.

High-end Risk Descriptor - A plausible estimate of the individual risk for those persons at the upper end of the risk distribution, conceptually above the 90th percentile but not higher than the individual in the population with the highest risk. Note that persons in the high end of the risk distribution have high risk due to high exposure, high susceptibility, or other reasons, and therefore persons in the high end of the exposure or dose distribution are not necessarily the same individuals as those in the high end of the risk distribution.

Intake - The process by which a substance crosses the outer boundary of an organism without passing an absorption barrier, e.g., through ingestion or inhalation. (See also potential dose)

Internal dose - The amount of a substance penetrating across the absorption barriers (the exchange boundaries) of an organism, via either physical or biological processes. For the purpose of these Guidelines, this term is synonymous with absorbed dose.

Limit of detection (LOD) [or Method detection limit (MDL)] - The minimum concentration of an analyte that, in a given matrix and with a specific method, has a 99% probability of being identified, qualitatively or quantitatively measured, and reported to be greater than zero.

Matrix - A specific type of medium (e.g., surface water, drinking water) in which the analyte of interest may be contained.

Maximally exposed individual (MEI) - The single individual with the highest exposure in a given population (also, maximum exposed individual). This term has historically been defined various ways, including as defined here and also synonymously with worst case or bounding estimate. Assessors are cautioned to look for contextual definitions when encountering this term in the literature.

Maximum exposure range - A semiquantitative term referring to the extreme uppermost portion of the distribution of exposures. For consistency, this term (and the dose or risk analogues) should refer to the portion of the individual exposure distribution that conceptually falls above about the 98th percentile of the distribution, but is not higher than the individual with the highest exposure.

Median value - The value in a measurement data set such that half the measured values are greater and half are less.

Microenvironment method - A method used in predictive exposure assessments to estimate exposures by sequentially assessing exposure for a series of areas (microenvironments) that can be approximated by constant or well-characterized concentrations of a chemical or other agent.

Microenvironments - Well-defined surroundings such as the home, office, automobile, kitchen, store, etc. that can be treated as homogeneous (or well characterized) in the concentrations of a chemical or other agent.

Mode - The value in the data set that occurs most frequently.

Monte Carlo technique - A repeated random sampling from the distribution of values for each of the parameters in a generic (exposure or dose) equation to derive an estimate of the distribution of (exposures or doses in) the population.

Nonparametric statistical methods - Methods that do not assume a functional form with identifiable parameters for the statistical distribution of interest (distribution-free methods).

Pathway - The physical course a chemical or pollutant takes from the source to the organism exposed.

Personal measurement - A measurement collected from an individual's immediate environment using active or passive devices to collect the samples.

Pharmacokinetics - The study of the time course of absorption, distribution, metabolism, and excretion of a foreign substance (e.g., a drug or pollutant) in an organism's body.

Point-of-contact measurement of exposure - An approach to quantifying exposure by taking measurements of concentration over time at or near the point of contact between the chemical and an organism while the exposure is taking place.

Potential dose - The amount of a chemical contained in material ingested, air breathed, or bulk material applied to the skin.

Precision - A measure of the reproducibility of a measured value under a given set of conditions.

Probability samples - Samples selected from a statistical population such that each sample has a known probability of being selected.

Quality assurance (QA) - An integrated system of activities involving planning, quality control, quality assessment, reporting and quality improvement to ensure that a product or service meets defined standards of quality with a stated level of confidence.

Quality control (QC) - The overall system of technical activities whose purpose is to measure and control the quality of a product or service so that it meets the needs of the users. The aim is to provide quality that is satisfactory, adequate, dependable, and economical.

Quantification limit (QL) - The concentration of analyte in a specific matrix for which the probability of producing analytical values above the method detection limit is 99%.

Random samples - Samples selected from a statistical population such that each sample has an equal probability of being selected.

Range - The difference between the largest and smallest values in a measurement data set.

Reasonable worst case - A semiquantitative term referring to the lower portion of the high end of the exposure, dose, or risk distribution. The reasonable worst case has historically been

loosely defined, including synonymously with maximum exposure or worst case, and assessors are cautioned to look for contextual definitions when encountering this term in the literature. As a semiquantitative term, it is sometimes useful to refer to individual exposures, doses, or risks that, while in the high end of the distribution, are not in the extreme tail. For consistency, it should refer to a range that can conceptually be described as above the 90th percentile in the distribution, but below about the 98th percentile. (Compare maximum exposure range, worst case).

Reconstruction of dose - An approach to quantifying exposure from internal dose, which is in turn reconstructed after exposure has occurred, from evidence within an organism such as chemical levels in tissues or fluids or from evidence of other biomarkers of exposure.

Representativeness - The degree to which a sample is, or samples are, characteristic of the whole medium, exposure, or dose for which the samples are being used to make inferences.

Risk - The probability of deleterious health or environmental effects.

Risk characterization - The description of the nature and often the magnitude of human or nonhuman risk, including attendant uncertainty.

Route - The way a chemical or pollutant enters an organism after contact, e.g., by ingestion, inhalation, or dermal absorption.

Sample - A small part of something designed to show the nature or quality of the whole. Exposure-related measurements are usually samples of environmental or ambient media, exposures of a small subset of a population for a short time, or biological samples, all for the purpose of inferring the nature and quality of parameters important to evaluating exposure.

Sampling frequency - The time interval between the collection of successive samples.

Sampling plan - A set of rules or procedures specifying how a sample is to be selected and handled.

Scenario evaluation - An approach to quantifying exposure by measurement or estimation of both the amount of a substance contacted, and the frequency/duration of contact, and subsequently linking these together to estimate exposure or dose.

Source characterization measurements - Measurements made to characterize the rate of release of agents into the environment from a source of emission such as an incinerator, landfill, industrial or municipal facility, consumer product, etc.

Standard operating procedure (SOP) - A procedure adopted for repetitive use when performing a specific measurement or sampling operation.

Statistical control - The process by which the variability of measurements or of data outputs of a system is controlled to the extent necessary to produce stable and reproducible results. To say

that measurements are under statistical control means that there is statistical evidence that the critical variables in the measurement process are being controlled to such an extent that the system yields data that are reproducible within well-defined limits.

Statistical significance - An inference that the probability is low that the observed difference in quantities being measured could be due to variability in the data rather than an actual difference in the quantities themselves. The inference that an observed difference is statistically significant is typically based on a test to reject one hypothesis and accept another.

Surrogate data - Substitute data or measurements on one substance used to estimate analogous or corresponding values of another substance.

Uptake - The process by which a substance crosses an absorption barrier and is absorbed into the body.

Worst case - A semiquantitative term referring to the maximum possible exposure, dose, or risk, that can conceivably occur, whether or not this exposure, dose, or risk actually occurs or is observed in a specific population. Historically, this term has been loosely defined in an ad hoc way in the literature, so assessors are cautioned to look for contextual definitions when encountering this term. It should refer to a hypothetical situation in which everything that can plausibly happen to maximize exposure, dose, or risk does in fact happen. This worst case may occur (or even be observed) in a given population, but since it is usually a very unlikely set of circumstances, in most cases, a worst-case estimate will be somewhat higher than occurs in a specific population. As in other fields, the worst-case scenario is a useful device when low probability events may result in a catastrophe that must be avoided even at great cost, but in most health risk assessments, a worst-case scenario is essentially a type of bounding estimate.

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PART B: RESPONSE TO PUBLIC AND SCIENCE ADVISORY BOARD COMMENTS

1. INTRODUCTION

This section summarizes the major issues raised in public comments on the Proposed Guidelines for Exposure-Related Measurements (hereafter "1988 Proposed Guidelines") published December 2, 1988 (53 FR 48830-48853). In addition to general comments, reviewers were requested to comment specifically on the guidance for interpreting contaminated blanks versus field data, the interpretation of data at or near the limit of detection, approaches to assessing uncertainty, and the Glossary of Terms. Comment was also invited on the following questions: Should the 1988 Proposed Guidelines be combined with the 1986 Guidelines for Estimating Exposures (hereafter "1986 Guidelines")? Is the current state-of-the-art in making measurements of population activities for the purpose of exposure assessment advanced to the point where the Agency can construct guidelines in this area? Given that EPA Guidelines are not protocols or detailed literature reviews, is the level of detail useful and appropriate, especially in the area of statistics?

The Science Advisory Board (SAB) met on December 2, 1988, and provided written comments in a May 1989 letter to the EPA Administrator (EPA-SAB-EETFC-89-020). The public comment period extended until March 2, 1989. Comments were received from 17 individuals or organizations.

After the SAB and public comment, Agency staff prepared summaries of the comments and analyses of major issues presented by the commentors. These were considered in the development of these final Guidelines. In response to the comments, the Agency has modified or clarified most of the sections of the Guidelines. For the purposes of this discussion, only the most significant issues reflected by the public and SAB comments are discussed. Several minor recommendations, which do not warrant discussion here, were considered and adopted by the Agency in the revision of these Guidelines.

The EPA revised the 1988 Proposed Guidelines in accordance with the public and SAB comments, retitling them Guidelines for Exposure Assessment (hereafter "Guidelines"). The Agency presented the draft final Guidelines to the SAB at a public meeting on September 12, 1991, at which time the SAB invited public comment for a period of 30 days on the draft. The SAB discussed the final draft in a January 13, 1992 letter to the Administrator of the EPA (EPA-SAB-IAQC-92-015). There were no additional public comments received.

2. RESPONSE TO GENERAL COMMENTS

In general, the reviewers were complementary regarding the overall quality of the 1988 Proposed Guidelines. Several reviewers requested that the Agency better define the focus and intended audiences and refine the Guidelines with regard to treatment of nonhuman exposure. The Agency has refined its approach and coverage in these Guidelines. Although these Guidelines deal specifically with human exposures to chemicals, additional supplemental guidance may be developed for ecological exposures, and exposures to biological or radiological entities. The Agency is currently developing separate guidelines for ecological risk assessment.

Concerns were expressed about the Agency's use of the terms exposure and dose. Consequently, the Agency reviewed its definitions and uses of these terms and evaluated their use elsewhere in the scientific community. The Agency has changed its definitions and uses of these terms from that in both the 1986 Guidelines and the 1988 Proposed Guidelines. It is believed that the definitions contained in the current Guidelines are now in concert with the definitions suggested by the National Academy of Sciences and others in the scientific field.

Many reviewers urged the Agency to be more explicit in its recommendations regarding uncertainty in statistics, limits of detection, censored data sets, and the use of models. Some reviewers felt the level of detail was appropriate for statistical uncertainty while others wanted additional methods for dealing with censored data. Several commended the Agency for its acknowledgement of uncertainty in exposure assessments and the call for its explicit description in all exposure assessments, while others expressed concern for lack of acknowledgement of model uncertainty. Accordingly, these areas have been revisited and an entire section has been devoted to uncertainty. We agree with the reviewers that much more work remains to be done in this area, particularly with evaluating overall exposure assessment uncertainty, not only with models but also with the distributions of exposure parameters. The Agency may issue additional guidance in this area in the future.

Some reviewers submitted extensive documentation regarding detection limits and statistical representations. Several submitted comments arguing against data reporting conventions that result in censored data sets and recommended that the Agency issue a guidance document for establishing total system detection limits. The Agency found the documentation to be helpful and has revised the sections of the Guidelines accordingly. Unfortunately, several of the other suggestions go beyond the scope of this document.

The reviewers generally commented that the glossary was useful, presenting many technical terms and defining them in an appropriate manner. The glossary has been expanded to include the key terms used in the Guidelines, while at the same time correcting some definitions

that were inconsistent or unclear. In particular, the definitions for exposure and dose have been revised.

3. RESPONSE TO COMMENTS ON THE SPECIFIC QUESTIONS

Should the 1988 Proposed Guidelines be combined with the 1986 Guidelines?

The SAB and several other commentors recommended that the 1986 Guidelines and the 1988 Proposed Guidelines be combined into an integrated document. The Agency agrees with this recommendation and has made an effort to produce a single guideline that progresses logically from start to finish. This was accomplished through an extensive reformatting of the two sets of guidelines as an integrated document, rather than a simple joining together of the previous versions.

In integrating the two previous guidelines, the Agency has revised and updated the section in the 1986 Guidelines that suggests an outline for an exposure assessment. A more complete section (Section 7 of the current Guidelines) now discusses how assessments should be presented and suggests a series of points to consider in reviewing assessments.

The Agency has also expanded the section in the 1986 Guidelines that discussed exposure scenarios, partly by incorporating material from the 1988 Proposed Guidelines, and partly as a result of comments requesting clarification of the appropriate use of certain types of scenario (e.g., "worst case"). Section 5.3 of the current Guidelines extensively discusses the appropriateness of using various scenarios, estimates, and risk descriptors, and defines certain scenario-related terms for use in exposure assessments.

Is the current state-of-the-art in making measurements of population activities for the purpose of exposure assessment advanced to the point where the Agency can construct guidelines in this area?

Both the SAB and public comments recommended the inclusion of demographics, population dynamics, and population activity patterns in the exposure assessment process. In response, the Agency has included additional discussion on use of activity patterns in the current Guidelines, while recognizing that more research has to be done in this area.

Is the level of detail of the Guidelines useful and appropriate, especially in the area of statistics?

As might be expected, there was no clear consensus of opinion on what constitutes appropriate coverage. Regarding quality assurance (QA) and quality control (QC), it was felt that a strong statement on the need for QA/QC followed by reference to appropriate EPA

documents was a suitable level of detail. Statistical analyses, sampling issues, limit of detection, and other analytical issues all elicited many thoughtful comments. Where the recommendations did not exceed the scope of the document or the role of EPA, the Agency has attempted to blend the various recommendations into the current Guidelines. In all these areas, therefore, the previous sections have been revised in accordance with comments.